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NUCYNTA® (Tapentadol) Extended-Release: Fourth Safety Surveillance Plan Progress Report

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Issue Date: 02 December 2013
Document No: EDMS-ERI-74585390

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1. INTRODUCTION

A Safety Surveillance Plan (SSP) for NUCYNTA® (tapentadol hydrochloride [HCl] extended-release [ER], hereafter referred to as tapentadol ER), was developed to monitor various safety activities. This is the fourth Safety Surveillance Plan (SSP) Progress Report for tapentadol ER.

The purpose of this document is to provide an update on the various activities described in the tapentadol ER SSP, as well as an evaluation of the data generated from these activities from each data source for the current review period. The reporting period covered is from 26 February 2013 through 25 August 2013. For each pharmacovigilance activity, this progress report presents a summary of the methods employed and an assessment of the safety data reviewed. The safety findings, including any newly identified potential safety signals that may warrant further investigation, are discussed within the context of the adequacy of the current SSP activities. Finally, the progress report provides an overall safety evaluation based on all SSP data sources and, if applicable, recommendations for modifications to the SSP.

According to the tapentadol ER SSP, data from SCEPTRE (the Global Medical Safety [GMS] safety database), the Food and Drug Administration's Adverse Event Reporting System/Spontaneous Reporting System (AERS+SRS[a]) (hereafter referred to as FDA AERS) database, RADARS® (Researched Abuse, Diversion, and Addiction-Related Surveillance System) Poison Control Center database and other RADARS® Signal Detection Systems (ie, Survey of Key Informants' Patients, Opioid Treatment Centers, Drug Diversion, and College Survey Programs) and NAVIPPRO® (National Addictions Vigilance Intervention and Prevention Program) Addiction Severity Index-Multimedia Version (ASI-MV®), Comprehensive Health Assessment for Teens (CHAT), and Web Informed Services (WIS) Internet Monitoring will be reviewed on a semi-annual basis.

a: Combined dataset containing reports within FDA's Spontaneous Reporting System (SRS; 1968-October 1997) and AERS (November 1997-present)

2. BACKGROUND

2.1. Product Description

Tapentadol is a centrally-acting synthetic analgesic combining opioid and non-opioid activities in a single molecule. It is 18 times less potent than morphine in binding to the human μ-opioid receptor and is 2 to 3 times less potent in producing analgesia in animal models. Unlike morphine, tapentadol has been shown to inhibit norepinephrine reuptake in the brains of rats, resulting in increased norepinephrine concentrations. In preclinical models, the analgesic activity due to the μ-opioid receptor agonist activity of tapentadol can be antagonized by selective μ-opioid receptor antagonists (eg, naloxone), whereas the norepinephrine reuptake inhibition is sensitive to norepinephrine modulators.[1]

According to the current United States Package Insert (USPI) dated August 2012, tapentadol ER is indicated for the management of moderate to severe chronic pain and neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. Dosages should be adjusted to the severity of the patient's pain, previous treatment experience, and the ability to monitor the patient. Oral tapentadol ER tablets are available in 50, 100, 150, 200, and 250 mg. The recommended oral starting dose in patients currently not taking opioid analgesics is 50 mg administered twice daily. After initiation of therapy, the dose should be titrated individually to a level that provides adequate analgesia and minimizes side effects under the close supervision of the prescribing physician. Experience from clinical trials has shown that a titration regimen in increments of 50 mg tapentadol twice daily every 3 days was appropriate to achieve adequate pain control in most of the patients. Total daily doses of tapentadol ER tablets greater than 500 mg tapentadol have not been studied and are therefore not recommended. During discontinuation, tapering of therapy is not required, but patients should be cautioned about the possibility of experiencing withdrawal symptoms.[2]

Tapentadol ER was approved by the United States (US) Food and Drug Administration (FDA) on 25 August 2011 and launched 03 September 2011. An additional indication for the management of neuropathic pain associated with DPN in adults was approved on 28 August 2012 (ER formulation in New Drug Application [NDA] 200533/S-001). Both the immediate-release and extended-release formulations of tapentadol are approved and marketed in various regions of the world, including Australia, Canada, the European

Union and the United States. Janssen Research & Development, L.L.C. and Grünenthal GmbH, the Company's development and marketing partner, share worldwide marketing rights. Janssen Pharmaceuticals, Inc (JPI) and Grünenthal each maintain a safety database for the product and cooperate to ensure that the safety information in both databases is consistent.

2.2. Safety Surveillance Plan Summary

The sections below summarize the key features and commitments from the tapentadol ER SSP.

2.2.1. Safety Surveillance Plan Version in Effect During Review Period

The tapentadol ER SSP in effect at the time of preparation of this progress report is dated 16 March 2011.

2.2.2. Summary of Safety Concerns

Risks that are regarded as medically important in general and/or for compounds with μ-opioid agonist activity are presented in Table 1, as they appear in the tapentadol ER SSP. Also included in this table, though not in the SSP, is serotonin syndrome which was raised by the FDA as a theoretical risk, particularly with concomitant use of serotonergic medications, during their medical review of the tapentadol Immediate Release (IR) application. In addition, events suggestive of choking, sticking, and esophageal obstruction are regarded as important potential risks because of the possibility that tamper-resistant formulation (TRF) tablets become sticky and expand upon getting moist and thus becoming difficult to swallow and a potential choking hazard.

Table 1: Summary of Safety Concerns for Tapentadol ER

Safety Concerns
Important identified risks:
Potential for abuse
Seizure
Important potential risks:
Overdose
Off-label use, including pediatric patients
Potential for medication errors (inappropriate prescribing, inappropriate dosing, inappropriate use) and patient misuse
Accidental exposure
Diversion
Serotonin syndrome[a]
Events suggestive of choking, sticking, and esophageal obstruction[b]
Important missing information:
Use in pediatrics
Use during pregnancy and lactation
Use in patients with renal impairment
Use in patients with hepatic impairment

Key: ER=Extended-release

a: Not in the tapentadol ER SSP, but raised by the FDA as a theoretical risk, particularly with concomitant use of serotonergic medications, during their medical review of the tapentadol IR application.

b: Not in the tapentadol ER SSP, but regarded as important potential risks because of the possibility that tamper-resistant formulation (TRF) tablets become sticky and expand upon getting moist and thus becoming difficult to swallow and a potential choking hazard.

The potential for abuse and seizure are regarded as important identified risks due to known class effects for substances with μ-opioid activity. In addition, 1 case of seizure was observed in a Phase 1 trial of tapentadol ER tablets. Although the subject had a history of seizures (seizure disorder was not well-controlled on valproate and not known to investigator at enrollment), it was decided to include this medical concept as an adverse drug reaction (ADR) in the label. Subjects with a history of seizures were excluded from all clinical studies. In addition, respiratory depression, manufacturing complaints, and all cases with a fatal outcome are monitored as part of the product specific surveillance plan.

During the clinical development of tapentadol ER, subjects less than 18 years of age were not studied. Therefore, the use of tapentadol ER in this population is not recommended.

2.2.3. Overview of the Pharmacovigilance Plan

The surveillance activities conducted by GMS for tapentadol ER comprise both routine surveillance activities, as well as product-specific activities, including descriptive summary statistics and trend analyses for the events of interest (safety concerns) identified in Table 1.

In addition to the GMS surveillance activities outlined in the SSP, Janssen Scientific Affairs (JSA) has entered into contracts with independent analysts to monitor selected events of interest related to abuse, misuse, and diversion of opioid medications (including NUCYNTA® ER). These contractors collect, compile, and analyze data pertaining to tapentadol ER obtained from supplementary RADARS® System and NAVIPPRO® programs to enhance the evaluation of these events. The results of the review of data from each of the surveillance activities for this progress report period are discussed in Section 3.1, Pharmacovigilance Plan.

2.3. Post-Marketing Exposure to Tapentadol (All Formulations)

Reporting frequencies calculated using exposure data do not reflect occurrence rates. Multiple factors influence the reporting of spontaneous experiences and therefore, caution must be exercised in the analysis and evaluation of spontaneous reports. In addition, product exposure is estimated at the time of distribution, not at the time of usage. There is a delay between the times a medication is distributed until it is used by a patient.

Patient exposure was estimated by calculation from company and partner distribution data. Estimates of exposure are based upon finished product. Based on IMS© National Prescription Audit (NPA) data, the average daily dose is 280 mg. Therefore, 280 mg is equivalent to 1 person-day.

Table 2: Exposure to Tapentadol (01 February 2013 to 31 August 2013)

Region	Grams	Person-days
U.S.A.	3,474,163	12,407,724

Based on the 3,474,163 grams of finished product distributed in the US by the company (from 01 February 2013 to 31 August 2013), the estimated exposure to tapentadol is 12,407,724 person-days.

Cumulative Exposure Estimate:

Table 3: Cumulative Exposure to Tapentadol (Launch to 31 August 2013)

Region	Grams	Person-days
U.S.A.	19,497,640	69,634,427

Based on the 19,497,640 grams of finished product distributed in the US by the company (from launch to 31 August 2013), the estimated exposure to tapentadol is 69,634,427 person-days

2.4. Regulatory Actions Taken in the Period Covered by This Report

Nothing to report.

2.5. Changes to the Reference Safety Information

Nothing to report.

2.6. Benefit Risk Analysis Reports Completed During the Period of Interest

Three benefit-risk analysis reports were completed during the period of interest (ie, 26 February 2013 to 25 August 2013).

2.6.1. Cumulative Review of Post-marketing Reports of Hypertension/Increased Blood Pressure in Patients Receiving NUCYNTA®/PALEXIA® (Tapentadol)

Hypertension and increased blood pressure (BP) were identified as safety signals for tapentadol based on increased reporting in SCEPTRE, the Global Medical Safety (GMS) database and disproportionate reporting in the Food and Drug Administration Adverse Events Reporting System database. The purpose of this report was to determine if there is a drug-event association between tapentadol and hypertension/increased blood pressure.[3]

A search of SCEPTRE was performed cumulatively through 30 September 2012 to retrieve all medically confirmed and non-medically confirmed, spontaneous valid cases received for tapentadol and reporting adverse events coded to the PTs included in the MedDRA (version 15.0) SMQ Hypertension. In addition, trends in systolic and diastolic BP from clinical trials of tapentadol immediate release (IR) and extended release (ER) formulations in acute and chronic pain and diabetic peripheral neuropathy were reviewed. The broad search of SCEPTRE for cases of hypertension/increased BP retrieved 82 cases. An aggregate case review identified that 44% (36/82) of the cases involved patients who were younger (<60 years) than the age when the prevalence of hypertension increases in the general population. In 28% (23/82) of the cases, the latency was either the same day or 1 day after initiating tapentadol. A case level review did not identify any cases that met the case definition for hypertension; therefore, all 82 cases were considered as increased BP cases. There were 9 cases that were selected for further review. These cases described a plausible latency and temporal relationship between exposure to tapentadol and increased BP in 9 cases, positive dechallenge in 7 cases and positive rechallenge in 1 case. However, 5 cases reported a potential confounder such as estradiol, a history

of hypertension (well controlled or baseline BP not provided) and/or nightmares or diverticulitis and colitis. Clinical trials involving both tapentadol IR and ER formulations did not demonstrate an increase in trend in the systolic and diastolic BP measurements in the tapentadol arm compared to placebo and active comparators for approved indications.[3]

It was hypothesized that blockade of norepinephrine (NE) transporters by norepinephrine reuptake inhibitors (NRI) could sensitize the heart to sympathetic activation (due to increase in NE levels), increasing cardiac output and leading to increased BP. It was believed that the likely mechanism of NRI-induced hypertension is the increase in levels of NE (due to NE reuptake inhibition) and the subsequent potentiation of noradrenergic neurotransmission. In addition, acute pain has been associated with increased BP secondary to generalized arousal and increased sympathetic nerve activity, whereas chronic pain may be associated with higher prevalence of hypertension possibly due to the altered relationship between the cardiovascular and pain regulatory systems.[3]

Based on the cumulative weight of evidence, it was concluded that there was no clear association identified between tapentadol and hypertension/increased BP. Key factors supporting this conclusion were 1 case of positive rechallenge with possible alternative explanation for the reported BP increase, 5 cases with potential confounders despite a close temporal association and/or positive dechallenge and cumulative evidence of well-controlled clinical trial data that did not demonstrate any increase in trend in BP with tapentadol.[3]

2.6.2. Cumulative Review of Panic Attack With the Use of Tapentadol Hydrochloride

Panic attack (PA) was identified as a safety signal for tapentadol, based on increased interval reporting during the routine SCEPTRE aggregate signal detection review, covering the period from 01 April 2012 to 30 June 2012.[4]

The purpose of this review was to determine whether there was sufficient evidence, from a review of the cumulative clinical trial and post-marketing cases reporting PA with the use of tapentadol, to suggest a drug-event association between tapentadol and PA.[4]

A search of clinical trial databases and SCEPTRE, the Global Medical Safety (GMS) safety database, was performed to identify all cases involving tapentadol, with adverse events coded to the Medical Dictionary for

Regulatory Activities (MedDRA; version 15.0) Preferred Term (PT) Panic attack.[4]

A review of the 13 cases identified from the clinical trial databases indicated that 6 cases (2 from acute pain studies and 4 from chronic pain studies) lacked alternative explanations for the PAs. The search of SCEPTRE retrieved 11 cases. Six of the 11 cases were eliminated from further review because of insufficient information (5 cases) or confounding medical history (1 case). The remaining 5 cases included 3 males and 2 females, with a mean age of 46 years. Of the 5 cases, 4 reported a plausible temporal relationship between the use of tapentadol and the event onset; 1 reported a plausible drug exposure history. All of the 5 cases reported symptoms consistent with the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) PA diagnosis criteria. In 2 cases, the event recurred with subsequent doses of tapentadol (positive rechallenge). A review of the 5 cases did not identify other risk factors proven to be associated with the PAs reported in these patients.[4]

Based on this cumulative review, the Company considers PA to be an adverse drug reaction (ADR) associated with the use of tapentadol. Key factors supporting this conclusion include a plausible temporal relationship and a lack of alternative explanations, positive rechallenge, and biological plausibility. In clinical trials, the incidence rate of PA associated with the use of tapentadol is 0.16% (13 cases per 7,969 subjects); the ADR frequency is estimated at 1.6 per 1,000 subjects, consistent with the CIOMS frequency of Uncommon or occurring at a frequency of ≥1/1,000 and <1/100. The post-marketing reporting frequency for PA is estimated at approximately 1 per 5,999,555 person-days, consistent with the CIOMS frequency of Very Rare or occurring at a frequency of <1/10,000.[4]

3. DATA REVIEW AND ANALYSES

3.1. Pharmacovigilance Plan

The surveillance activities conducted by GMS for tapentadol ER comprise both routine surveillance activities and product-specific activities. The latter includes descriptive summary statistics and trend analyses for the events of interest identified in the tapentadol ER SSP, and events reported in special populations (ie, pediatric patients and patients who are pregnant or lactating). These activities are performed using SCEPTRE and the FDA AERS database. In addition, the Company contracts with outside vendors who collect, compile, and analyze data regarding tapentadol ER obtained from the

supplementary RADARS® and NAVIPPRO® programs. The most current information available for each data source was reviewed. The periodicity and dates of the current review period for each surveillance activity included in this report are summarized in Table 4.

Table 4: Data Source Review Periods for Tapentadol ER Safety Surveillance Plan Progress Report

Data Source	Frequency of Review	Latest Review Period	Cumulative Review Period
Routine Surveillance			
SCEPTRE			
Intra-Product Signaling	Every 6 months	01 January 2013 to 30 June 2013	26 August 2011[a] to 30 June 2013
QA Lot Review	Every 6 months[b]	01 January 2013 to 30 June 2013 Cumulative to 2012Q3	26 August 2011[a] to 30 June 2013
FDA AERS Data Mining	Every 6 months		Cumulative to 2012Q3
Product-Specific Surveillance			
SCEPTRE			
Summary Statistics[c]	Every 6 months	26 February 2013 to 25 August 2013	26 August 2011[a] to 25 August 2013
Trend Analysis	Every 6 months	26 February 2013 to 25 August 2013	26 August 2011[a] to 25 August 2013
FDA AERS			
Summary Statistics[c]	Every 6 months	Cumulative to 2012Q4	Cumulative to 2012Q4
RADARS® Systems Programs			
Opioid Treatment Program	Every 3 months	01 October 2012 to 30 June 2013	01 October 2011 to 30 June 2013
Drug Diversion Network	Every 3 months	01 October 2012 to 30 June 2013	01 July 2011 to 30 June 2013
Key Informant Network	Every 3 months	01 October 2012 to 30 June 2013	01 October 2011 to 30 June 2013
Poison Center Network	Every 3 months	01 October 2012 to 30 June 2013	01 July 2011 to 30 June 2013
College Survey Program	Three times per year	01 October 2012 to 31 March 2013	01 July 2011 to 31 March 2013
Field Research Activities	As needed[d]	N/A	N/A
NAVIPPRO® System Programs			
ASI_MV	Every 4 months	01 January 2013 to 30 April 2013	01 January 2012 to 30 April 2013
CHAT	Every 4 months	01 January 2013 to 30 April 2013	01 January 2012 to 30 April 2013
WIS	Every 4 months	01 January 2013 to 30 April 2013	01 January 2012 to 30 April 2013

Table 4: Data Source Review Periods for Tapentadol ER Safety Surveillance Plan Progress Report

Key: ASI-MV= Addiction Severity Index Multimedia Version; CHAT= Comprehensive Health Assessment for Teens; ER=Extended-release; FDA AERS=Food and Drug Administration's Adverse Event Reporting System; JSA=Janssen Scientific Affairs; N/A Not Applicable; NAVIPPRO= National Addictions Vigilance Intervention and Prevention Program; Q=Quarter; QA=Quality Assurance; RADARS= Researched Addiction-Related Surveillance; SCEPTRE=Global Medical Safety database; WIS= Web Informed Services

a: For the purpose of this report, the first day following the US approval of tapentadol ER (25 August 2011) was used as initial day of the cumulative reporting period.

b: QA Lot Review data routinely became available along with quarterly scheduled Intra-Product Signaling data beginning 13 March 2012; prior to this, it was performed as an independent review every 6 months.

c: Includes both case counts and demographics.

d: Field Research completed as recommended by Pinney Associates and approved by JSA.

3.1.1. Routine Surveillance Activities

3.1.1.1. Introduction

This section summarizes the surveillance activities and findings for the fourth Safety Surveillance Plan Progress Report for tapentadol ER. Surveillance activities summarized in this report for tapentadol ER are those performed by GMS and include both routine and product-specific surveillance activities. Both routine and product-specific activities are conducted on spontaneous reports in SCEPTRE and in FDA AERS.

Any worldwide, spontaneous case reporting any formulation of tapentadol received by the Company or the Company's development partner, Grünenthal, is included in SCEPTRE.

Routine surveillance activities for tapentadol ER include real-time review of AE data as well as scheduled reviews of aggregated AE data. This report summarizes the scheduled reviews of aggregated AE data. Routine, scheduled surveillance activities for tapentadol ER include: intra-product signaling to monitor for changes in AE reporting frequencies and patterns; a Quality Assurance (QA) lot review to monitor for potential product quality concerns; and reviews of alerts generated to identify potential safety and/or product quality signals associated with product lots on a real-time basis. Each of these activities is performed using data from SCEPTRE. Routine surveillance activities for tapentadol ER also include data mining of FDA AERS.

The routine aggregate signal detection review includes an analysis of aggregate worldwide data for all formulations of tapentadol and subgroup analyses of aggregate worldwide data for tapentadol IR and tapentadol ER.

Routine surveillance activities performed using FDA AERS data include all spontaneous worldwide cases reporting the generic names tapentadol or tapentadol extended-release as suspect or suspect-interacting drug.

3.1.1.2. Review of SCEPTRE Data

SCEPTRE is a centralized and validated safety database that contains spontaneous AE reports and serious AE reports from clinical trials. SCEPTRE contains AE information received by the Company from multiple sources including health care professionals, clinical trial investigators, literature reports, regulatory agencies, solicited programs (eg, registries), and consumers.

In addition, SCEPTRE contains AE information reported with product quality complaints; however, all product quality complaints received by the Company with or without an AE are contained within a separate product quality database. As the product quality database may be considered the most complete source for such reports, caution is advised when considering the results of reviews of AE information reported with product quality complaints within this surveillance report as they are based on SCEPTRE data only.

3.1.1.2.1. Objectives

The objectives of the aggregate, routine SCEPTRE surveillance activities are:

- To identify and assess relative changes in reporting frequency or patterns of AEs and AE groupings for a Company product over time that may suggest potential safety or product quality signals.
- To identify lots with disproportionate reporting of AE groupings that are suggestive of potential product quality concerns.

3.1.1.2.2. Methods, Intra-Product Signaling Review and Lot Alert Review

As part of routine surveillance, aggregate data from all spontaneously reported cases in SCEPTRE that include tapentadol ER as a suspect or suspect-interacting drug are reviewed every calendar quarter to identify relative changes in reporting frequency or patterns of AEs and AE groupings. This review compares the reporting percentage for each Medical Dictionary for Regulatory Activities (MedDRA) PT and selected AE groupings (ie, all MedDRA High Level Terms, Designated Medical Events [DMEs] and selected designated medical groupings based on SMQs) in the current period with that of the same PT or AE grouping in the previous period. The reporting percentage of a PT or AE grouping is defined as the number of cases reporting a specific PT or AE grouping for the product in a given period divided by the total number of cases reporting any AE for the same product in the same period multiplied by 100. The comparison between the current and the previous period's reporting percentage is based on the fractional reporting ratio (FRR) for each PT and AE grouping. The FRR is calculated by dividing the reporting percentage for a given PT (or AE grouping) in the current period by the reporting percentage of that same PT (or AE grouping) in the previous period. All PTs and AE groupings reported

during the current period, including those with an incalculable FRR[b] and those reported in more than 3 cases with an FRR ≥2, are assessed to determine if they may represent a new safety concern that may warrant further evaluation. Graphs of reporting trends (reporting percentage by reporting period) are reviewed as necessary to determine if there were any reporting trends requiring further review. All DMEs, such as but not limited to toxic epidermal necrolysis, Stevens-Johnson syndrome, and aplastic anemia, are considered as part of this review regardless of their reporting frequency.

Routine surveillance also includes a review of all AE cases reported in SCEPTRE with lot numbers. This QA Lot Review is an aggregate review performed to identify potential product quality concerns through examination of AE reporting patterns in a given lot, or lots disproportionately reported with AE groupings targeted for product quality monitoring.[c]

Prior to 13 March 2012, the QA Lot Review occurred every 6 months, independently of the intra-product signaling review. SCEPTRE was queried for any spontaneous cases reporting a lot number and tapentadol as a suspect or suspect-interacting drug during the 6-month period, and the data was presented in a freestanding report and analyzed as such. Medical review of this data occurred if at least 1 lot had 3 or more cases reported cumulatively, and a new case reported during the current period. Commencing 13 March 2012, the QA Lot data was entered in and analyzed along with the routine intra-product signaling information. Each reported lot/AE pair is reviewed to determine if the number or type of AEs reported with each lot is suggestive of a potential quality concern. In addition, a cumulative reporting percentage for each lot/AE grouping pair reported during the current period is calculated and compared with the cumulative reporting percentage for the same AE grouping for all lots to determine whether the AE grouping is reported disproportionately with the lot.

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b: This occurs when there are no reports of the given PT or AE grouping during the previous period.

c: Accidental exposure, death, device malfunction, effectiveness decreased, effectiveness increased, medication errors, product contamination and sterility, product label issues, product packaging issues, product physical issues, product quality issues (not elsewhere classified), smell complaints, and taste complaints

On 01 April 2012, an alert system was instituted. This system generates an alert whenever a MedDRA High Level Term or other AE grouping is reported disproportionately with a product lot, as compared with all other lots of the product. These calculations occur and lot alerts are produced on a weekly basis.

Any lot/AE or lot/AE grouping pair suggestive of a potential new quality concern detected from the above reviews is communicated to Janssen Supply Chain (JSC) for further evaluation.

Since the previous progress report for tapentadol ER, one intra-product signaling review has been performed; a summary of conclusions from this review is included in this report. It examined AE frequencies and patterns during the 6-month period of 01 January 2013 to 30 June 2013,[d] and compared them with those of the immediate previous 6-month period.

3.1.1.2.3. Conclusions, Intra-Product Signaling Reviews and Lot Alert Reviews

Intra-product signaling review and lot alert reviews from 01 January 2013 to 30 June 2013, identified no new validated signals requiring further evaluation.

3.1.1.3. Review of the FDA AERS Database

The FDA AERS database contains all AE information reported to the FDA on products approved for marketing in the US. This includes all AE reports submitted by manufacturers as specified by federal regulations, US spontaneous reports received directly from health care professionals or consumers, and serious unexpected non-US reports where the US prescribing information is the reference safety document.

d: Surveillance data file 193 tapentadol hydrochloride 01 January 2013 to 30 June 2013 run date 01 July 2013

3.1.1.3.1. Objectives

The objectives of the routine FDA AERS surveillance activities are:

- To identify AEs that are reported disproportionately with the Company product compared to all other drugs in the FDA AERS database.
- To identify new potential safety concerns that may need additional evaluation, including further review of the Company database.

3.1.1.3.2. Methods

Data mining serves as a screening method for identifying potential safety concerns based on disproportionate reporting of AEs for tapentadol relative to all other drugs in the FDA AERS database. Disproportionate reporting of a particular PT is defined as the situation in which the following statistical criteria are met for that PT: (1) the Empirical Bayesian Geometric Mean (EBGM) for the PT is 2.0 or higher; (2) the lower limit of the 90% confidence interval (CI) for the EBGM is greater than 1.0; and (3) a minimum of 3 cases are reported for the PT. The review of events is particularly focused on unlisted PTs that have biological plausibility as adverse drug reactions. If a disproportionately reported AE warrants further evaluation, a case series from SCEPTRE is reviewed to determine if the AE is suggestive of a new safety concern.

Since the previous progress report for tapentadol ER, the FDA AERS database has been data mined once using Empirica™ Signal, Version 7.3 (Oracle, Inc.) to generate the EBGM statistic, with stratification by age, sex, and year of FDA receipt of the report. This data mining review utilized FDA AERS data through 2012Q3.

3.1.1.3.3. Conclusions

The data mining review of the FDA AERS 2012Q3 configuration identified no new validated signals requiring further evaluation.

3.1.2. Product-Specific Surveillance Activities

Product-specific surveillance activities for tapentadol ER are directed at the events of interest identified in its SSP and listed in Table 5. Although serotonin syndrome was not specifically targeted for monitoring in the tapentadol ER SSP, it was raised by the FDA as a theoretical risk, particularly with concomitant use of serotonergic medications, during their medical review of the tapentadol IR application. Therefore, it is also

monitored in product-specific surveillance as an event of interest for tapentadol ER.

Product-specific surveillance activities for tapentadol ER include descriptive summary statistics for cases in SCEPTRE and FDA AERS reporting events of interest identified in the tapentadol ER SSP. Product-specific surveillance activities also include trend analyses and analyses of case details for cases in SCEPTRE reporting tapentadol SSP events of interest.

3.1.2.1. Objective

The objectives of the tapentadol ER product-specific surveillance activities are:

- To monitor the number of spontaneous reports for each event of interest in SCEPTRE and the FDA AERS database.
- To monitor the demographic characteristics of patients who experienced events of interest reported spontaneously in SCEPTRE and the FDA AERS database.
- To monitor trends in spontaneous reporting for events of interest in SCEPTRE.

3.1.2.2. Methods

3.1.2.2.1. Identification of Cases

Aside from the exceptions noted in this section, cases reporting an event of interest with tapentadol ER were identified using PT groupings. Each tapentadol ER SSP event of interest or event subcategory corresponds to a grouping of MedDRA PTs. Table 5 summarizes each tapentadol ER SSP event of interest or event subcategory and its corresponding MedDRA PTs. These MedDRA PTs were used to query for cases reporting each SSP event of interest or event subcategory.

The SSP events of interest Drug abuse and Intentional misuse are presented together within this report. This combination was based on the assessment that the MedDRA PTs within both represent similar medical concepts for opioid products including tapentadol ER.

Cases with a fatal outcome were identified in SCEPTRE by the outcome of the case rather than by the events reported. Within the FDA AERS database, cases with a fatal outcome may be reported in various ways. Due to this

variability, cases with a fatal outcome were identified in the FDA AERS database if the outcome of the case was fatal or if the event Death was reported as a PT within the case.

Cases of tapentadol ER use in the pediatric population were identified as follows: In SCEPTRE, cases reporting tapentadol ER use in patients less than 18 years of age, with or without an adverse event, may be captured with the PT Off-label use. However, it is possible that Off-label use may be used in SCEPTRE to code an event other than use of tapentadol ER in patients less than 18 years of age. As the FDA AERS database may contain tapentadol ER reports that did not originate from the Company, it is possible that some cases in the FDA AERS database reporting tapentadol ER use in patients less than 18 years of age may not be coded as Off-label use. Thus, to assure completeness in monitoring of use in patients less than 18 years old within SCEPTRE and the FDA AERS database, cases of tapentadol ER use in patients less than 18 years of age were identified as follows: A search of SCEPTRE and AERS was performed to identify cases meeting any of the following criteria: Age group 0-17 years or Age <18 years.

Cases of tapentadol ER use during pregnancy and lactation were identified as follows: A search of SCEPTRE was performed to identify cases meeting any of the criteria below[e]; Classification Pregnancy Exposure/Pregnancy = Yes, or Special Grouped Criteria Pregnancy Exposure/Pregnancy = Yes, or Classification Parent/Child = Yes, or Age <3 years, or Age Group = Neonate or Infant, or SOC = Congenital, Familial And Genetic Disorders (Primary & Secondary Path), or SOC = Pregnancy, Puerperium And Perinatal Conditions (Primary & Secondary Path). FDA AERS does not contain searchable data fields which can identify cases of pregnancy or breast feeding; the AERS cases were manually reviewed to identify PTs which were consistent with pregnancy or breast feeding.

At the time of the database queries for this report, both SCEPTRE and FDA AERS data were coded to MedDRA, version 16.0. However, the software used to extract the SCEPTRE data contained MedDRA version 15.1. The SCEPTRE data was initially retrieved using MedDRA 15.1 terms and an

e: Global Medical Safety GDL-06433: Guideline for Aggregate Analysis of Drug Exposure During Pregnancy, V.2, Effective date 15 November 2012.

additional direct search of SCEPTRE was performed using the newly available MedDRA 16.0 PTs. Case lists were manually reviewed in order to ensure that no cases were included twice.

Table 5: MedDRA Preferred Terms Corresponding to SSP Events of Interest for Tapentadol ER

SSP Event of Interest	Description of Event or Event Subcategory	MedDRA PT(s)
Accidental exposure	*Accidental exposure*	Accidental drug intake by child[a] Accidental exposure[a] Accidental exposure to product[b] Accidental exposure to product by child[b] Exposure during breast feeding Exposure during pregnancy[b] Exposure via blood Exposure via direct contact Exposure via father Exposure via partner Exposure via semen[a] Exposure via vaginal fluid[a] Exposure via body fluid[b] Foetal exposure during delivery Foetal exposure during pregnancy Foetal exposure timing unspecified Maternal exposure during delivery Maternal exposure during pregnancy Maternal exposure before pregnancy Maternal exposure timing unspecified Failure of child resistant mechanism for pharmaceutical product Maternal drugs affecting foetus Occupational exposure to drug[a] Occupational exposure to product[b]Paternal drugs affecting foetus
Addiction	*Addiction*	Dependence Drug dependence Drug dependence, antepartum Drug dependence, postpartum Polysubstance dependence

Table 5: MedDRA Preferred Terms Corresponding to SSP Events of Interest for Tapentadol ER

SSP Event of Interest	Description of Event or Event Subcategory	MedDRA PT(s)
Choking	*Events suggestive of choking, sticking, and esophageal obstruction*	Asphyxia Choking Choking sensation Dysphagia Dysphonia Foreign body Foreign body aspiration Laryngeal discomfort[b] Laryngeal pain[b] Odynophagia Oesophageal discomfort Oesophageal disorder Oesophageal injury Oesophageal obstruction Oesophageal pain Oropharyngeal discomfort Oropharyngeal pain Pharyngeal injury Removal of foreign body from oesophagus Removal of foreign body from throat Throat irritation
Death	*Cases with a fatal outcome*	See description of search methods in Section 3.1.2.2.1
Diversion	*Diversion*	Drug diversion Prescription form tampering Product tampering
Drug abuse and Intentional misuse[c]	*Drug abuse and Intentional misuse*	Device Misuse Drug abuse Drug abuser Ex-drug abuser Intentional drug misuse Intentional overdose Multiple drug overdose intentional[d] Substance abuse

Table 5: MedDRA Preferred Terms Corresponding to SSP Events of Interest for Tapentadol ER

SSP Event of Interest	Description of Event or Event Subcategory	MedDRA PT(s)
Misuse[c]	*Off-label use*[d] *Medication errors*	Off-label use Circumstance or information capable of leading to medication error Counterfeit drug administered Documented hypersensitivity to administered drug Drug administered at inappropriate site Drug administered to patient of inappropriate age Drug administration error Drug dispensing error Drug dose omission Drug label confusion Drug name confusion Drug prescribing error Expired drug administered Inappropriate schedule of drug administration Incorrect dose administered Incorrect drug administration duration Incorrect drug administration rate Incorrect drug dosage form administered Incorrect route of drug administration Intercepted drug administration error Intercepted drug dispensing error Intercepted drug prescribing error Intercepted medication error Labeled drug-disease interaction medication error Labeled drug-drug interaction medication error Labeled drug-food interaction medication error Medication error Poor quality drug administered Prescribed overdose[b] Prescribed underdose[b] Product dosage form confusion Treatment noncompliance Wrong drug administered Wrong technique in drug usage process
Overdose	*Overdose*	Accidental overdose Accidental poisoning Analgesic drug level above therapeutic Drug level above therapeutic Multiple drug overdose[a] Multiple drug overdose accidental[a] Overdose Prescribed overdose[b] Toxicity to various agents

Table 5: MedDRA Preferred Terms Corresponding to SSP Events of Interest for Tapentadol ER

SSP Event of Interest	Description of Event or Event Subcategory	MedDRA PT(s)
Pediatric cases	*Pediatric cases*	See description of search methods in Section 3.1.2.2.1
Pregnancy and lactation	*Pregnancy and lactation*	See description of search methods in Section 3.1.2.2.1
Potential manufacturing complaint	*Decreased potency and Increased Potency*	Analgesic drug level below therapeutic Analgesic drug level decreased Drug effect decreased Drug effect delayed Drug half-life reduced Drug ineffective Drug ineffective for unapproved indication Drug level below therapeutic Drug level decreased No therapeutic response Therapeutic product ineffective Therapeutic product ineffective for unapproved indication Therapeutic reaction time decreased Therapeutic response decreased Therapeutic response delayed Treatment failure Analgesic drug level above therapeutic Analgesic drug level increased Drug effect increased Drug effect prolonged Drug half-life increased Drug level above therapeutic Drug level increased Therapeutic response increased Therapeutic response prolonged

Table 5: MedDRA Preferred Terms Corresponding to SSP Events of Interest for Tapentadol ER

SSP Event of Interest	Description of Event or Event Subcategory	MedDRA PT(s)
Respiratory depression	*Respiratory depression*	Acute respiratory failure Apnoea Apnoeic attack Bradypnoea Central-alveolar hypoventilation End-tidal CO_2 increased Hypercapnia Hypercapnic coma Hypopnoea Hypoventilation Hypoventilation neonatal Hypoxic-ischaemic encephalopathy Infantile apnoeic attack Neonatal respiratory acidosis Neonatal respiratory arrest Neonatal respiratory depression Neonatal respiratory failure Oxygen saturation decreased PCO_2 increased Respiratory acidosis Respiratory arrest Respiratory depression Respiratory depth decreased Respiratory failure Respiratory fatigue Respiratory paralysis Respiratory rate decreased

Table 5: MedDRA Preferred Terms Corresponding to SSP Events of Interest for Tapentadol ER

SSP Event of Interest	Description of Event or Event Subcategory	MedDRA PT(s)
Seizures	*Seizures*	Acquired epileptic aphasia Alcoholic seizure Atonic seizure Atypical benign partial epilepsy Automatism epileptic Autonomic seizure Baltic myoclonic epilepsy Benign familial neonatal convulsions Biotinidase deficiency Clonic convulsion Complex partial seizures Convulsion Convulsion in childhood Convulsion neonatal Convulsions local Convulsive threshold lowered Déjà vu Dreamy state Drug withdrawal convulsions Early infantile epileptic encephalopathy with burst suppression Eclampsia Epilepsy Epileptic aura Epileptic psychosis Febrile convulsion Frontal lobe epilepsy Generalised non-convulsive epilepsy Grand mal convulsion Hyperglycaemic seizure Hypoglycaemic seizure Hyponatraemic seizure[b] Infantile spasms Lafora's myoclonic epilepsy Lennox-Gastaut syndrome Myoclonic epilepsy Myoclonic epilepsy and ragged-red fibers Partial seizures Partial seizures with secondary generalisation Petit mal epilepsy Postictal headache Postictal paralysis Postictal state Post-traumatic epilepsy Psychomotor seizures Seizure anoxic Seizure cluster Simple partial seizures Status epilepticus Sudden unexplained death in epilepsy Temporal lobe epilepsy Tonic clonic movements Tonic convulsion Uncinate fits

Table 5: MedDRA Preferred Terms Corresponding to SSP Events of Interest for Tapentadol ER

SSP Event of Interest	Description of Event or Event Subcategory	MedDRA PT(s)
Serotonin syndrome[e]	*Serotonin syndrome*	Serotonin syndrome Serum serotonin increased

Key: CO_2=Carbon dioxide; ER= Extended-release; MedDRA=Medical Dictionary for Regulatory Activities; PCO_2=Partial pressure of carbon dioxide; SSP=Safety Surveillance Plan; PT=Preferred Term

a:Term available only in MedDRA 15.1

b: Term available only in MedDRA 16.0

c: The event subcategories for these events of interest (Drug abuse and Intentional misuse, Off-label use and Medication errors) reflect misuse as defined in the tapentadol ER SSP (ie, "use inconsistent with labeling whether intentional or unintentional").

d: Event of interest includes reports of use in patients <18 years of age.

e: This event was not specifically targeted for monitoring in the tapentadol ER SSP, but was raised by the FDA as a theoretical risk, particularly with concomitant use of serotonergic medications, during their medical review of the tapentadol IR application. Therefore, it is also monitored in product-specific surveillance as an event of interest.

3.1.2.2.2. Database Searches

3.1.2.2.2.1. SCEPTRE

Empirica™ Signal was used to query SCEPTRE data for the latest version of all spontaneous cases for which tapentadol ER was reported as a suspect or suspect-interacting medication.[f] Because cases from Company-sponsored/supported, non-interventional studies (eg, registries, patient assistance programs, epidemiological programs) are solicited or stimulated rather than true spontaneous reports, they were excluded from the search. Among these solicited cases are those originating from programs such as the RADARS program. Cases reporting an event of interest were identified using the PTs/strategies noted in Section 3.1.2.2.1 of this report. When case-level review was necessary within this report, version specific case numbers were used for retrieval of the cases from SCEPTRE.

This search was designed to capture cases initially received by the Company from 26 August 2011[g] through 25 August 2013.

f: Support Desk ticket number SDE00024766, dated 01 October 2013.

g: The first day following the US approval of tapentadol ER

3.1.2.2.2.2. FDA AERS

The FDA AERS database, containing data through the fourth quarter of 2012, was queried using Empirica™ Signal for all spontaneous cases for which tapentadol ER was listed as a suspect or suspect-interacting medication.[h] The search was designed to capture all cases initially received by the FDA on or after 26 August 2011.[i] Cases reporting an event of interest were identified using the PTs/strategies noted in Section 3.1.2.2.1 of this report.

3.1.2.2.3. Analyses

3.1.2.2.3.1. Tabulation of Case Counts and Review of Patient Populations of Interest

The number of cases in SCEPTRE and the FDA AERS database for each SSP event of interest by the calendar quarter during which the case was initially received is presented in tabular format and reviewed within this progress report. Within this report, the 2011Q3 refers to SCEPTRE cases initially received from 26 August 2011 through 30 September 2011, 2011Q4, 2012Q1, 2012Q2, 2012Q3, 2012Q4, 2013Q1, and 2013Q2 include full periods of data, and 2013Q3 includes cases initially received up to 25 August 2013. FDA AERS case counts available for this report include those through 2012Q4. Case counts between SCEPTRE and FDA AERS cannot be directly compared. Differences in case counts between SCEPTRE and FDA AERS data may be due to a number of factors, including but not necessarily limited to, time between Company submission and posting in AERS, and vendor trade name/formulation data cleaning algorithms. To provide a context for interpreting these raw case counts, the reporting percentage for each event of interest is included in the tabular results; this was calculated by dividing the number of US tapentadol ER cases initially received during a quarter that reported the event of interest by the total number of US tapentadol ER cases initially received during the same quarter reporting any event, then multiplying by 100.

For each SSP event of interest, a cumulative demographic analysis of age distribution and sex distribution for cases in SCEPTRE and the FDA AERS database is presented in tabular format and reviewed within the progress report. Cumulative dates for these analyses were 26 August 2011 through

h: Support Desk ticket number SDE00024766, dated 01 October 2013.

25 August 2013 for SCEPTRE and 26 August 2011 through 31 December 2012 for the FDA AERS database. To provide a context for interpreting the raw case counts provided in the age and sex distribution tabulations, the total number of cases reporting and not reporting age and sex for each event of interest is included as well as the percentage of cases reported for each age group and sex for each event of interest.

3.1.2.2.3.2. Case Series Analyses

A case series analysis for cases in SCEPTRE reporting selected events of interest is performed as required by the SSP. For cases of seizure, serotonin syndrome, or events suggestive of choking, sticking, and esophageal obstruction, and cases involving pediatric patients or pregnant/lactating women, the tapentadol ER indications, doses, and administration frequency, as well as the patients' medical histories, concomitant medications, and outcomes are tabulated and reviewed to determine if they suggest a change in the nature or severity of the event of interest.

3.1.2.2.3.3. Reporting Trend Analyses

A reporting-trend analysis of SCEPTRE data is performed for each SSP event of interest or event subcategory listed in Table 5 for which 5 or more cases have been reported cumulatively. Graphs of reporting percentage by reporting quarter for each SSP event of interest or event subcategory are reviewed to determine the reporting trend.

The 95% CIs[i] of reporting percentages are included in the graphs as a measure of their variability. The reporting percentage of a given period for a given event of interest is considered significantly different from that of a preceding period when the confidence intervals of the reporting percentages do not overlap. Reporting trends are classified as ascending, descending, stable (flat or nearly flat trend), or indeterminate (variability in trend and/or low case counts prevent clear visualization of the reporting trend). The consistency in the direction of change of reporting percentages in the graph and the extent of overlapping of their CIs are taken into account in determining reporting trends.

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i: Exact Binomial Confidence Intervals

3.1.2.2.4. Results

3.1.2.2.4.1. Tabulation of Case Counts in SCEPTRE and the FDA AERS Database by Event of Interest

The number of spontaneous US tapentadol ER cases in SCEPTRE for each event of interest and event subcategory is summarized in Table 6 by the quarter during which the case was initially received. It should again be noted that the 2011Q3 refers to case counts from 26 August 2011 to 30 September 2011 only, and 2013Q3 refers to case counts from 01 July 2013 to 25 August 2013 only.

Table 6: Number of US Spontaneous Tapentadol ER Cases in SCEPTRE by Event of Interest and by Quarter During Which the Case was Initially Received (2011Q3 Through 2013Q3)

Event of Interest	Description of Event[a]	2011Q3[b] N (%[c])	2011Q4 N (%[c])	2012Q1 N (%[c])	2012 Q2 N (%[c])	2012 Q3 N (%[c])	2012 Q4 N (%[c])	2013 Q1 N (%[c])	2013 Q2 N (%[c])	2013 Q3[f] N (%[c])	Total N (%[c])
Accidental exposure	*Accidental exposure*	0	1(1)	0	1 (1)	0	0	0	0	0	2 (<1)
Addiction	*Addiction*	0	0	0	1 (1)	0	1(2)	0	0	0	2 (<1)
Choking	*Choking*	0	0	1 (1)	1 (1)	1 (1)	2 (4)	0	0	0	5 (1)
Death	*Cases with a fatal outcome*	0	0	2 (3)	1 (1)	1 (1)	1 (2)	1 (2)	0	0	6 (1)
Diversion	*Diversion*	0	0	0	0	1 (1)	1 (2)	1 (2)	0	0	3 (<1)
Drug abuse and Intentional misuse	*Drug abuse and Intentional misuse*	0	0	0	1 (1)	0	1 (2)	0	0	2 (5)	4 (<1)
Misuse	*Off-label use*[d]	0	0	0	0	2 (2)	0	3 (6)	2 (5)	0	7 (1)
	Medication errors	2 (15)	3 (4)	7 (9)	12 (13)	8 (9)	5 (10)	11 (22)	12 (31)	11 (30)	71 (13)
Overdose	*Overdose*	0	0	1 (1)	4 (4)	4 (5)	0	5 (10)	0	0	14 (3)
Pediatric cases	*Pediatric cases*	0	0	0	1 (1)	0	1 (2)[f]	0	0	0	2 (<1)
Pregnancy and lactation	*Pregnancy and lactation*	0	1 (1)	0	0	0	1 (2)[g]	0[h]	0	0	2 (<1)
Potential manufacturing complaint	*Decreased potency*	3 (23)	17 (21)	25 (31)	17 (19)	17 (20)	11 (21)	21 (41)	5 (13)	14 (38)	130 (25)
	Increased potency	0	0	3 (4)	0	1 (1)	0	0	2 (5)	1 (3)	7 (1)
Respiratory depression	*Respiratory depression*	1 (8)	1 (1)	1 (1)	1 (1)	1 (1)	0	0	0	0	5 (1)
Seizures	*Seizures*	0	0	2 (3)	1 (1)	2 (2)	1 (2)	0	1 (3)	0	7 (1)
Serotonin syndrome	*Serotonin syndrome*	0	2 (3)	6 (7)	2 (2)	7 (8)	1 (2)	1 (2)	0	2 (5)	21 (4)
Total number of cases reporting any adverse event with tapentadol ER, including those not specified as an event of interest in the tapentadol ER SSP		**13 (100)**	**80 (100)**	**81 (100)**	**89 (100)**	**86 (100)**	**52 (100)**	**51 (100)**	**39 (100)**	**37 (100)**	**528 (100)**

Table 6: Number of US Spontaneous Tapentadol ER Cases in SCEPTRE by Event of Interest and by Quarter During Which the Case was Initially Received (2011Q3 Through 2013Q3)

Key: ER=Extended-release; N=Number of cases for a given period; Q=Quarter; SCEPTRE=Global Medical Safety database; SSP=Safety Surveillance Plan; US=United States

a: A single case may contain multiple adverse events within the same or a different event of interest subcategory

b: 2011Q3 encompasses the period 26 August 2011 through 30 September 2011.

c: Quarterly Reporting Percentage: The number of cases initially received during the quarter reporting the event of interest, divided by the total number of cases initially received during the same quarter reporting any adverse event multiplied by 100.

d: Counts for this event of interest in SCEPTRE may include, but may not be limited to, cases reporting the PT Off label use to indicate use in patients <18 years of age.

e: 2013Q3 encompasses the report period 26 February 2013 to 25 August 2013 only.

f: One case (20121006121) reporting an event of breast feeding reported multiple patients whose mothers were treated with tapentadol hydrochloride (drug exposure via breast milk). This case was retrieved in the Pregnancy search but is counted here as a Pediatric case and not as a Pregnancy and lactation case

g: One case (20121006036) reporting an event of medication error only was not captured by the SCEPTRE search for Pregnancy and lactation; this is the maternal case linked to 20120106121.This case reports multiple patients treated with tapentadol hydrochloride while they were breastfeeding. This case was included in the Pregnancy and lactation case count.

h: One case (20130206776) reporting the PT Failure to thrive reported a 61 year-old patient and was retrieved in this search because this PT is included in the Pregnancy Puerperium and Perinatal Conditions SOC. This case was not included in the case count.

The most frequently reported events of interest in SCEPTRE for tapentadol ER during 2013Q2 and 2013Q3 are decreased potency and medication errors. The reporting trends for the events of interest are further reviewed in Section 3.1.2.2.4.5.4 of this report.

The number of spontaneous US tapentadol ER cases in the FDA AERS database for each event of interest and event subcategory is summarized in Table 7. This includes cases initially received by the FDA from 26 August 2011 through 31 December 2012; FDA AERS data was available only through 2012Q4.

Table 7: Number of US Spontaneous Tapentadol ER Cases in the FDA AERS Database by Event of Interest and by the Quarter During Which the Case was Initially Received by the FDA (2011Q3 Through 2012Q4)

Event of Interest	Description of Event[a]	2011Q3[b] N (%[c])	2011Q4 N (%[c])	2012Q1 N (%[c])	2012Q2 N (%[c])	2012Q3 N (%[c])	2012Q4 N (%[c])	Total N (%[c])
Accidental exposure	*Accidental exposure*	0	0	0	0	0	0	0
Addiction	*Addiction*	0	0	0	0	0	0	0
Choking	*Choking*	0	0	0	0	1 (3)	0	1 (<1)
Death	*Cases with a fatal outcome*	0	0	2 (8)	3 (8)	1 (3)	2 (22)	8 (7)
Diversion	*Diversion*	0	0	0	0	1 (3)	0	1 (<1)
Drug abuse and Intentional misuse	*Drug abuse and Intentional misuse*	0	0	0	2 (5)	1 (3)	1 (11)	4 (3)
Misuse	*Off-label use*	0	0	0	0	0	0	0
	Medication errors	1 (100)	0	2 (8)	2 (5)	3 (10)	0	8 (7)
Overdose	*Overdose*	0	0	2 (8)	2 (5)	1 (3)	1 (11)	6 (5)
Pediatric cases	*Pediatric cases*	0	0	0	0	0	0[d]	0
Pregnancy and lactation	*Pregnancy and lactation*	0	0	0	0	0		0
Potential manufacturing complaint	*Decreased potency*	0	0	7 (29)	4 (10)	2 (7)	0	13 (11)
	Increased potency	0	0	0	0	0	0	0
Respiratory depression	*Respiratory depression*	0	0	2 (8)	1 (3)	2 (7)	1 (11)	6 (5)
Seizures	*Seizures*	0	0	1 (4)	1 (3)	0	1 (11)	3 (3)
Serotonin syndrome	*Serotonin syndrome*	0	0	5 (21)	3 (8)	6 (20)	1 (11)	15 (13)
Total number of cases reporting any adverse event with tapentadol ER, including those not specified as an event of interest in the tapentadol ER SSP		**1 (100)**	**16 (100)**	**24 (100)**	**40 (100)**	**30 (100)**	**9 (100)**	**120 (100)**

Table 7: Number of US Spontaneous Tapentadol ER Cases in the FDA AERS Database by Event of Interest and by the Quarter During Which the Case was Initially Received by the FDA (2011Q3 Through 2012Q4)

Key: ER=Extended-release; FDA=Food and Drug Administration; FDA AERS=Food and Drug Administration's Adverse Event Reporting System; N=Number of cases for a given period; Q=Quarter; SSP=Safety Surveillance Plan

a: A single case may contain multiple adverse events within the same or a different event of interest subcategory.
b: 2011Q3 encompasses the period 26 August 2011 through 30 September 2011.
c: Quarterly Reporting Percentage: The number of cases initially received during the quarter reporting the event of interest, divided by the total number of cases initially received during the same quarter reporting any adverse event multiplied by 100.
d: Search returned 2 cases which upon review were found to not represent use in age <18 years

The quarterly number of spontaneous cases in the FDA AERS database reporting any AE for tapentadol ER has slowly and steadily increased. While the low number of cases reported for each event of interest within the FDA AERS database for tapentadol ER limits analyses, it can be noted that decreased potency and serotonin syndrome account for the largest number of spontaneous cases reported within this database.

There are 2 cases reporting use of tapentadol ER in a patient less than 18 years in the FDA AERS database as of 31 December 2012. These correspond to SCEPTRE cases 20121000120 and 20121106470, both of which report on a woman in her sixth decade; these represent examples of the aforementioned discrepancies between SCEPTRE and FDA AERS data.

3.1.2.2.4.2. Age Distributions in SCEPTRE and the FDA AERS Database by Event of Interest

The number of US spontaneous tapentadol ER cases reported in SCEPTRE for each event of interest and event subcategory is summarized by age group in Table 8. This is a cumulative tabulation that includes cases initially received from 26 August 2011 through 25 August 2013.

Table 8: Number of US Spontaneous Tapentadol ER Cases in SCEPTRE by Event of Interest and by Age Group Cumulatively, 26 August 2011 Through 25 August 2013

Event of Interest	Event Subcategory[a]	Number (%[b]) of Cases by Age Group in Years					Total Number of Cases With Known Age	Total Number of Cases With Unknown Age
		0 to 11 N (%)	12 to 17 N (%)	18 to 40 N (%)	41 to 65 N (%)	>65 N (%)		
Accidental exposure	*Accidental exposure*	0	1 (50)	1 (50)	0	0	2	0
Addiction	*Addiction*	0	0	0	0	1 (100)	1	1
Choking	*Choking*	0	0	0	3 (100)	0	3	2
Death	*Cases with a fatal outcome*	0	0	1 (33)	2 (67)	0	3	3
Diversion	*Diversion*	0	0	0	0	1 (100)	1	2
Drug abuse and Intentional misuse	*Drug abuse and Intentional misuse*	0	0	0	2 (67)	1 (33)	3	1
Misuse	*Off-label use*[c]	1 (14)[d]	0	1 (14)	2 (29)	3 (43)	7	1
	Medication errors	0	0	11 (26)	24 (56)	8 (19)	43	28
Overdose	*Overdose*	0	0	3 (43)	2 (29)	2 (29)	7	7
Pregnancy and lactation	*Pregnancy and lactation*	0	0	1 (50)	1 (50)	0	2	1[e]
Potential manufacturing complaint	*Decreased potency*	0	0	16 (20)	49 (61)	15 (19)	80	50
	Increased potency	0	0	1 (50)	1 (50)	0	2	5
Respiratory depression	*Respiratory depression*	0	0	0	2 (100)	0	2	3
Seizures	*Seizures*	0	0	1(100)	0	0	1	6
Serotonin syndrome	*Serotonin syndrome*	0	0	4 (44)	2 (22)	3 (33)	9	12
Total number of cases reporting any adverse event with tapentadol ER, including those not specified as an event of interest in the tapentadol ER SSP		**1 (1)**	**1 (1)**	**70 (29)**	**129 (53)**	**44 (18)**	**245**	**284**

Table 8: Number of US Spontaneous Tapentadol ER Cases in SCEPTRE by Event of Interest and by Age Group Cumulatively, 26 August 2011 Through 25 August 2013

Key: ER=Extended-release; N=Number of cases for a given age; SCEPTRE=Global Medical Safety database; SSP=Safety Surveillance Plan; US= United States

a: A single case may contain multiple adverse events within the same or a different event of interest subcategory.

b: Percentage of the total number of cases with known age for each event of interest.

c: Counts for this event of interest in SCEPTRE include, but may not be limited to, cases reporting the PT Off-label use to indicate use in patients <18 years of age.

d: One case (20121006121) reporting an event of breast feeding reported multiple patients whose mothers were treated with tapentadol hydrochloride (drug exposure via breast milk).

e: One case (20121006036) reporting an event of medication error was not captured by the SCEPTRE search for Pregnancy and lactation; this is the maternal case linked to 20120106121.This case reports multiple patients treated with tapentadol hydrochloride while they were breastfeeding. This case was included in the Pregnancy and lactation case count.

Cumulatively, age has been reported in 46.3 % (245/529) of all US spontaneous tapentadol ER cases in SCEPTRE. For events of interest with at least 5 cumulative cases reporting a known age as well as for cases reporting any adverse events, the most commonly reported age group is the 41 to 65 year-old age group.

The number of spontaneous tapentadol ER cases reported in the FDA AERS database for each event of interest and event subcategory is summarized by age group in Table 9. This tabulation includes cases initially received by the FDA from 26 August 2011 through 31 December 2012.

Table 9: Number of US Spontaneous Tapentadol Extended-Release Cases in the FDA AERS Database by Event of Interest and by Age Group (2011Q3 Through 2012Q4)

Event of Interest	Event Subcategory[a]	Number (%[b]) of Cases by Age Group in Years					Total Number of Cases With Known Age	Total Number of Cases With Unknown Age
		0 to 11 N (%)	12 to 17 N (%)	18 to 40 N (%)	41 to 65 N (%)	>65 N (%)		
Accidental exposure	*Accidental exposure*	0	0	0	0	0	0	0
Addiction	*Addiction*	0	0	0	0	0	0	0
Choking	*Choking*	0	0	0	1 (100)	0	1	0
Death	*Cases with a fatal outcome*	0	0	2 (50)	2 (50)	0	4	4
Diversion	*Diversion*	0	0	0	0	0	0	1
Drug abuse and Intentional misuse	*Drug abuse and Intentional misuse*	0	0	0	3 (100)	0	3	1
Misuse	*Off-label use*	0	0	0	0	0	0	0
	Medication errors	0	0	0	4 (67)	2 (33)	6	2
Overdose	*Overdose*	0	0	2 (40)	3 (60)	0	5	1
Pregnancy and lactation	*Pregnancy and lactation*	0	0	0	0	0	0	0
Potential manufacturing complaint	*Decreased potency*	0	0	1 (9)	10 (91)	0	11	2
	Increased potency	0	0	0	0	0	0	0
Respiratory depression	*Respiratory depression*	0	0	0	4 (80)	1 (20)	5	1
Seizures	*Seizures*	0	0	0	2 (100)	0	2	1
Serotonin syndrome	*Serotonin syndrome*	0	0	2 (18)	4 (36)	5 (45)	11	4
Total number of cases reporting any adverse event with tapentadol ER, including those not specified as an event of interest in the tapentadol ER SSP		**2 (2)**	**0 (0)**	**19 (23)**	**49 (60)**	**12 (15)**	**82**	**36**

Key: ER=Extended-release; FDA AERS=Food and Drug Administration's Adverse Event Reporting System; N=Number of cases for a given age; Q=Quarter; SSP=Safety Surveillance Plan

a: A single case may contain multiple adverse events within the same or a different event of interest subcategory.

b: Percentage of the total number of cases with known age for each event of interest.

Cumulatively, age has been reported in 70.0% (82/118) of all spontaneous tapentadol ER cases in the FDA AERS database. While the relatively small number of cases precludes comparison between age groups for individual events of interest, the available data does reveal that the most commonly reported age groups for spontaneous cases reporting any adverse event with tapentadol ER in the FDA AERS database are the 18 to 40 and 41 to 65 year-old age groups.

3.1.2.2.4.3. Sex Distributions in SCEPTRE and the FDA AERS Database by Event of Interest

The number of US spontaneous tapentadol ER cases reported in SCEPTRE for each event of interest and event subcategory is summarized by sex in Table 10. This is a cumulative tabulation that includes cases initially received from 26 August 2011 through 25 August 2013.

Table 10: Number of US Spontaneous Tapentadol ER Cases in SCEPTRE by Event of Interest and by Sex (26 August 2011 Through 25 August 2013)

Event of Interest	Event Subcategory[a]	Male N (%[b])	Female N (%[b])	Female to Male Ratio	Number of Cases With Known Sex	Number of Cases With Unknown Sex
Accidental exposure	*Accidental exposure*	1 (50)	1 (50)	1	2	0
Addiction	*Addiction*	1 (50)	1 (50)	1	2	0
Choking	*Choking*	2 (67)	1 (33)	0.5	3	2
Death	*Cases with a fatal outcome*	0	3 (100)	N/A	3	3
Diversion	*Diversion*	3 (100)	0	0	3	0
Drug abuse and Intentional misuse	*Drug abuse and Intentional misuse*	2 (67)	1 (33)	0.5	3	1
Misuse	*Off-label use*[c]	5 (71)	2 (29)	0.4	7	0
	Medication errors	28 (47)	32 (53)	1.1	60	11
Overdose	*Overdose*	5 (50)	5 (50)	1	10	4
Pediatric cases	*Pediatric cases*	1 (100)	0	0	1	0
Pregnancy and lactation	*Pregnancy and lactation*	0	3 (100)	N/A	3	0
Potential manufacturing complaint	*Decreased potency*	38 (34)	75 (66)	2	113	17
	Increased potency	2 (40)	3 (60)	1.5	5	2
Respiratory depression	*Respiratory depression*	0	4 (100)	N/A	4	1
Seizures	*Seizures*	1 (20)	4 (80)	4	5	2
Serotonin syndrome	*Serotonin syndrome*	10 (59)	7 (41)	0.7	17	4
Total number of cases reporting any adverse event with tapentadol ER, including those not specified as an event of interest in the tapentadol ER SSP		**163 (39)**	**257 (61)**	**1.6**	**420**	**108**

Table 10: Number of US Spontaneous Tapentadol ER Cases in SCEPTRE by Event of Interest and by Sex (26 August 2011 Through 25 August 2013)

Key: ER=Extended-release; N=Number of cases for a given sex; N/A=Not applicable; SCEPTRE=Global Medical Safety database; SSP=Safety Surveillance Plan; US=United States

a: A single case may contain multiple adverse events within the same or a different event of interest subcategory.

b: Percentage of the total number of cases with known sex for each event of interest.

c: Counts for this event of interest in SCEPTRE include, but may not be limited to, cases reporting the PT Off-label use to indicate use in patients <18 years of age

Cumulatively, sex has been reported in 79.5% (420/528) of all spontaneous tapentadol ER cases in SCEPTRE. The most frequently reported sex in SCEPTRE for spontaneous tapentadol ER cases reporting any adverse event, as well as most of the events of interest with at least 5 cumulative cases reporting the patient's sex, is female. The exception to this is serotonin syndrome, which was reported slightly more often in males than females.

The number of spontaneous tapentadol ER cases reported in the FDA AERS database for each event of interest and event subcategory is summarized by sex in Table 11. This tabulation includes cases initially received by the FDA from 26 August 2011 through 31 December 2012.

Table 11: Number of US Spontaneous Tapentadol Extended-Release Cases in the FDA AERS Database by Event of Interest and by Sex (26 August 2011 Through 31 December 2012)

Event of Interest	Event Subcategory [a]	Male N (%[b])	Female N (%[b])	Female to Male Ratio	Number of Cases With Known Sex	Number of Cases With Unknown Sex
Accidental exposure	*Accidental exposure*	0	0	0	0	0
Addiction	*Addiction*	0	0	0	0	0
Choking	*Choking*	1 (100)	0	0	1	0
Death	*Cases with a fatal outcome*	2 (40)	3 (60)	1.5	5	3
Diversion	*Diversion*	1 (100)	0	0	1	0
Drug abuse and Intentional misuse	*Drug abuse and Intentional misuse*	1 (33)	2 (67)	2	3	1
Misuse	*Off-label use*	0	0	0	0	0
	Medication errors	2 (33)	4 (67)	2	6	2
Overdose	*Overdose*	0	5 (100)	NA	5	1
Pediatric cases	*Pediatric cases*	0	0[d]	NA	2	0
Pregnancy and lactation	*Pregnancy and lactation*	0	0	0	0	0

Table 11: Number of US Spontaneous Tapentadol Extended-Release Cases in the FDA AERS Database by Event of Interest and by Sex (26 August 2011 Through 31 December 2012)

Event of Interest	Event Subcategory [a]	Male N (%[b])	Female N (%[b])	Female to Male Ratio	Number of Cases With Known Sex	Number of Cases With Unknown Sex
Potential manufacturing complaint	*Decreased potency*	5 (42)	7 (58)	1.4	12	1
	Increased potency	0	0	0	0	0
Respiratory depression	*Respiratory depression*	2 (40)	3 (60)	1.5	5	1
Seizures	*Seizures*	1 (33)	2 (67)	2	3	0
Serotonin syndrome	*Serotonin syndrome*	10 (71)	4 (29)	0.4	14	1
Total number of cases reporting any adverse event with tapentadol ER, including those not specified as an event of interest in the tapentadol ER SSP		**41 (39)**	**65 (61)**	**1.6**	**106**	**12**

Key: ER=Extended-release; FDA AERS=Food and Drug Administration's Adverse Event Reporting System; N=Number of cases for a given sex; N/A=Not applicable; SSP=Safety Surveillance Plan
a: A single case may contain multiple adverse events within the same or a different event of interest subcategory.
b: Percentage of the total number of cases with known sex for each event of interest.
c: Case 20111109733 reported PT Exposure during pregnancy.
d: Search returned 2 cases which upon review were found to not represent use in age <18

Cumulatively, sex was reported in 89.8% (106/118) of all spontaneous tapentadol ER cases in the FDA AERS database. The most frequently reported sex in spontaneous cases reporting any adverse event with tapentadol in the FDA AERS database is female. Serotonin syndrome is an exception to this general trend and was reported approximately 2 times more frequently in males than females.

3.1.2.2.4.4. Case Series Analysis of SCEPTRE Cases

The following sections summarize cases reporting events suggestive of choking, sticking or esophageal obstruction, cases involving the pediatric population or pregnant/lactating women, and cases of seizure or serotonin syndrome in SCEPTRE that were received during the current progress report period (26 February 2013through 25 August 2013). Analyses of relevant US cases include tabulations of tapentadol ER indications, doses and frequency as well as patient's medical histories, concomitant medications, and outcomes. Cases are further analyzed to consider if they suggest a change in the nature, severity, or outcome of the event of interest.

3.1.2.2.4.4.1. Choking

Events suggestive of choking, sticking, and esophageal obstruction are regarded as important potential risks in the tapentadol ER SSP because of a concern regarding whether TRF tablets become sticky and expand upon getting moist, and the related potential to cause a potential choking hazard or difficulty swallowing.

During the current progress report period (26 February 2013 through 25 August 2013), there were no initial US spontaneous cases reporting events suggestive of choking, sticking, and esophageal obstruction.

3.1.2.2.4.4.2. Pediatric Use

During the current progress report period (26 February 2013 through 25 August 2013), there were no initial US spontaneous cases reporting use of tapentadol ER in the pediatric population.

3.1.2.2.4.4.3. Use in Pregnancy and Lactation

During the current progress report period (26 February 2013 through 25 August 2013), there was 1 US spontaneous case returned in the search for cases reporting use of tapentadol ER during pregnancy. Case 20130206776 reported Failure to thrive in a 61 year old female who was treated with tapentadol ER for metastatic breast cancer pain. This case is not related to pregnancy but was captured in the search for Pregnancy and Lactation as the PT "Failure To Thrive" is in the "Pregnancy, Puerperium, and Perinatal Conditions" SOC. This case will not be discussed further.

3.1.2.2.4.4.4. Seizure

The current US labeling for tapentadol ER states, *"NUCYNTA® ER has not been evaluated in patients with a predisposition to a seizure disorder, and such patients were excluded from clinical studies. The active ingredient tapentadol in NUCYNTA® ER may aggravate convulsions in patients with convulsive disorder and may induce or aggravate seizures in some clinical settings. Monitor patients with a history of seizure disorders for worsened seizure control during NUCYNTA® ER therapy."* This section summarizes cases of seizure with tapentadol ER that were received during the current progress report period and assesses the consistency of such reports with the above labeling.

During the current progress report period (26 February 2013 through 25 August 2013), 1 initial US spontaneous case reporting seizure with tapentadol ER was received. Case 20130516428 described a patient (age and

sex not reported) with a history of seizures who experienced a possible seizure after the start of tapentadol therapy. Details including latency since the start of tapentadol therapy, tapentadol dosage, concomitant medications, and medical history were not provided, precluding an accurate medical assessment.

In summary, there was 1 spontaneous case in SCEPTRE reporting seizures with the use of tapentadol ER received during the current progress report period. The case contained insufficient information for assessment against the current US label for tapentadol ER. Review of this case did not suggest a new safety concern.

3.1.2.2.4.4.5. Serotonin Syndrome

Serotonin syndrome is listed under the Warnings and Precautions section of the current US label for tapentadol ER, but is included in the SSP as it was raised by the FDA as a theoretical risk during the FDA's medical review of the tapentadol IR application, particularly with concomitant use of serotonergic medications. The current US labeling for tapentadol ER states "*Cases of life-threatening serotonin syndrome have been reported with the concurrent use of tapentadol and serotonergic drugs. Serotonergic drugs comprise Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, drugs that affect the serotonergic neurotransmitter system (e.g. mirtazapine, trazodone, and tramadol), and drugs that impair metabolism of serotonin (including MAOIs). This may occur within the recommended dose."* This section summarizes cases reporting serotonin syndrome with tapentadol ER that were received during the current progress report period and assesses the consistency of such reports with the above labeling.

During the current progress report period (26 February 2013 through 25 August 2013), 3 (1 follow-up, 2 initial) US spontaneous cases reporting serotonin syndrome with tapentadol ER were received. The single follow-up case (20120212637) provided no new significant safety information, and 1 initial case (20130803215) involved multiple unidentifiable patients with no details, including tapentadol dose, latency, details of the event, and outcome. These 2 cases are not further discussed. The remaining case is presented below.

- **20130801586[j] (Serotonin syndrome; Drug interaction):** A 39-year-old male with a history of childhood seizures was treated with tapentadol 200 mg daily for chronic back pain. Co-suspect drug was venlafaxine 75 mg daily for "many years." Concomitant medications were not reported. After a "recent" switch from oxycodone/acetaminophen to tapentadol, the patient was admitted to the hospital twice within 12 days for symptoms of total body tremors, anxiety and excessive sedation (reported as possible serotonin syndrome). It was reported that the total body tremors were not apparent seizures, and the patient remained conscious throughout these episodes. During the first admission the patient also experienced chills, diarrhoea, and severe headache. Tapentadol therapy was discontinued. Results of an electrocardiogram, computerized tomogram, chest x-ray, and cardiolite stress test were negative. He was discharged after 2 days, and resumed therapy with tapentadol and venlafaxine. Ten days after discharge, he was hospitalized with the same symptoms, and a drug interaction between tapentadol and venlafaxine was suspected. Both medications were discontinued. The events were resolving at the time of discharge 2 days later.

Overall, only 1 case (20130801586) received during the current progress report period provided sufficient information for an accurate medical assessment. The description of the events in this case does not meet the criteria for clinically significant serotonin syndrome as required by the Hunter Serotonin Toxicity diagnostic criteria[5] (ie, no reported clonus or hyperreflexia). Tremor and anxiety are listed ADRs in the US label for both tapentadol and venlafaxine[k] so an additive effect may have played a role in the development of the events; sedation is known to occur with tapentadol. The tapentadol dosage was consistent with the approved dosage in the US label, and the events resolved with discontinuation of therapy.

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j: Michael A. Mancano. ISMP Adverse Drug Reactions: Serotonin syndrome with concomitant use of tapentadol and venlafaxine. *Hospital Pharmacy*. 2013;48 (7): 542-549.

k: Effexor (venlafaxine). http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020151s031s055s058s060lbl.pdf. Accessed 18 October 2013.

In summary, only 1 spontaneous case in SCEPTRE reporting serotonin syndrome with the use of tapentadol ER that was received during the current progress report period contained sufficient information. The information provided was consistent in nature, severity, and outcome with the current US label for the product. Review of this case did not suggest a new safety concern.

3.1.2.2.4.5. SCEPTRE Reporting Trend Analyses by Event of Interest

The following subsections summarize the trends in reporting percentages for events of interest and event subcategories listed in Table 5 for US tapentadol ER spontaneous cases in SCEPTRE with an initial receipt date of 26 August 2011 through 25 August 2013. In the context of these reporting trend analyses, reporting quarter should be understood to mean the calendar quarter during which a case was initially received by the Company. As the start date (26 August 2011) and stop date (25 August 2013) of the report do not coincide with the start and stop dates of their respective calendar quarters, the data from 2011Q3 and 2013Q3 do not represent data from an entire quarter.

Reporting percentage graphs for events of interest are only included in this report if at least 5 or more cases have been reported in SCEPTRE cumulatively for that event of interest. This number was chosen as it was felt to represent the minimal number of cases necessary to establish a baseline or analyze a reporting trend. Thus a trend line is included for Choking, Fatal cases, Off label use, Medication errors, Overdose, Decreased potency, Increased potency, Respiratory depression, Seizures, and Serotonin syndrome (see Table 6).

3.1.2.2.4.5.1. Trend Analysis – Choking

Figure 1 displays the reporting percentage by reporting quarter for choking. Since US product launch, there have been 5 cases that reported choking. The reporting percentage for choking was zero to 4% in all 9 quarters since launch; the overall pattern is stable.

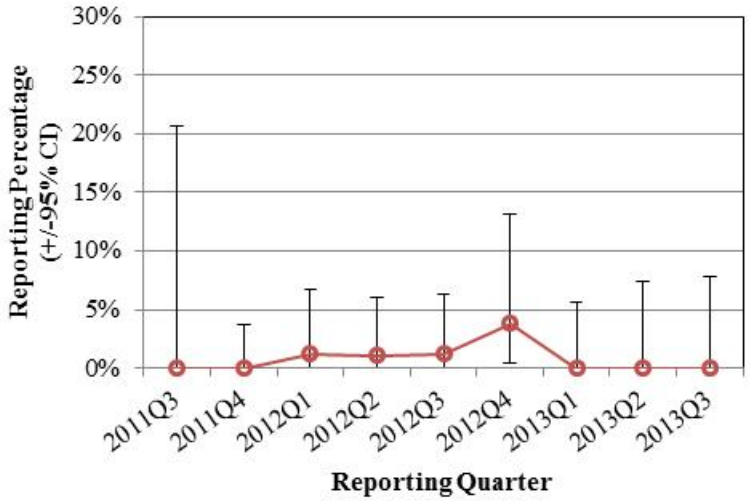

Figure 1: Reporting Percentage of US tapentadol ER Cases in SCEPTRE by Reporting Quarter – Choking.

3.1.2.2.4.5.2. Trend Analysis – Cases With Fatal Outcome

Figure 2 displays the reporting percentage by reporting quarter for cases with fatal outcome. Since US product launch, there have been 6 cases that reported a fatal outcome. The reporting percentage for fatal cases was zero to 3% in all 9 quarters. The reporting trend for cases with fatal outcome is stable.

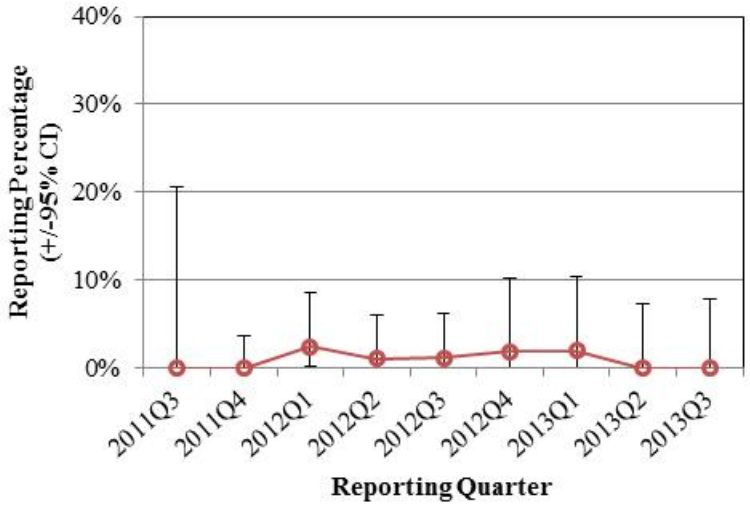

Figure 2: Reporting Percentage of tapentadol ER Cases in SCEPTRE by Reporting Quarter – Cases with Fatal Outcome.

3.1.2.2.4.5.3. Trend Analysis – Off-label Use

Figure 3 displays the reporting percentage by reporting quarter for off-label use. Since US product launch, there have been 7 cases that reported off-label use. The reporting percentage for off-label use was zero to 2% in the first 6 quarters since launch, increased in 2013Q1 (6%) and 2013Q2 (5%) and was again zero in 2013Q3. The overall pattern is indeterminate.

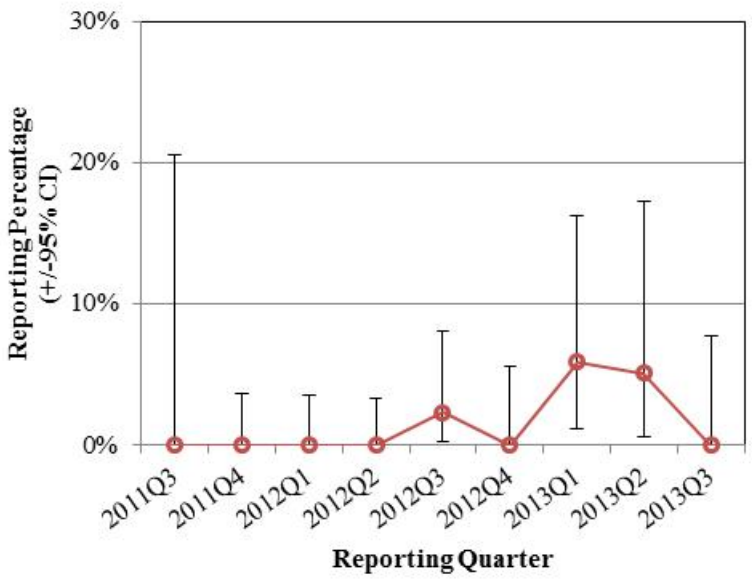

Figure 3: Reporting Percentage of US Tapentadol ER Cases in SCEPTRE by Reporting Quarter – Off-label Use.

3.1.2.2.4.5.4. Trend Analysis – Medication Errors

Figure 4 displays the reporting percentage by reporting quarter for medication errors. Since US product launch, there have been 71 cases that reported medication errors. The reporting percentage for medication errors was between 4% and 15% in the first 6 quarters after launch and increased to approximately 20-30% the last 3 quarters (2013Q1, 2013Q2 and 2013Q3).

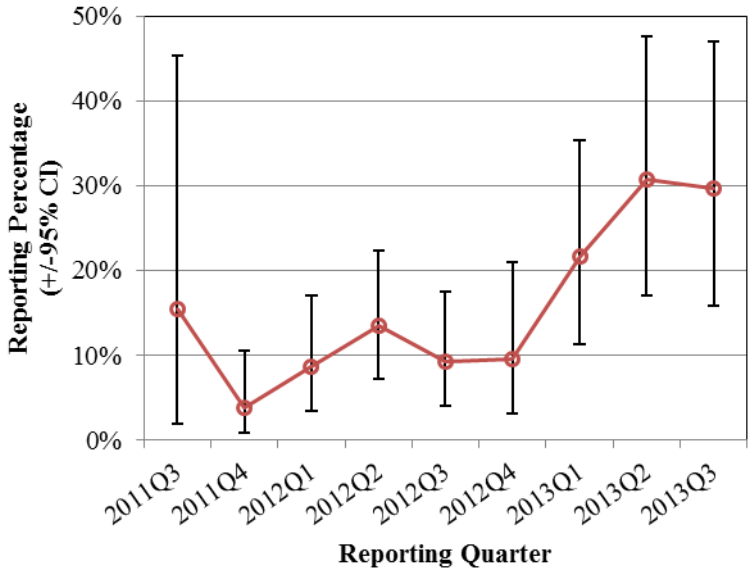

Figure 4: Reporting Percentage of US Tapentadol ER Cases in SCEPTRE by Reporting Quarter - Medication Errors.

The overall trend for Medication Errors appears to be increasing. This is likely related to recent changes in case processing conventions, which include a greater emphasis on capturing medication errors and maladministrations.

The cases received during the first 3 quarters of 2013 were reviewed. There are 34 cases reporting 38 Medication errors. Twenty two of the 34 events describe the patient missing a dose for various reasons; the most common reason was the inability to find a pharmacy which had the medication available, but other reasons included that the patient ran out of medication, and that insurance would not pay for the drug. There were 3 cases of Wrong technique in drug usage process, in which the patient was splitting the tablets; 3 cases of Treatment noncompliance, where the patient took fewer tablets than prescribed, and 3 cases of Drug prescribing error, all of which described a different scenario. There were 2 cases in which tapentadol IR was either prescribed or administered rather than tapentadol ER, which was intended. The remaining 5 cases did not demonstrate any patterns of medication errors. The descriptions in these cases do not represent a new safety signal.

3.1.2.2.4.5.5. Trend Analysis – Overdose

Figure 5 displays the reporting percentage by reporting quarter for overdose. Since US product launch, there have been 14 cases that reported overdose. The reporting percentage for overdose was zero to 5% in the first 6 quarters after launch, doubled in 2013Q1, and was again zero in 2013Q2 and 2013Q3. The overall pattern is indeterminate.

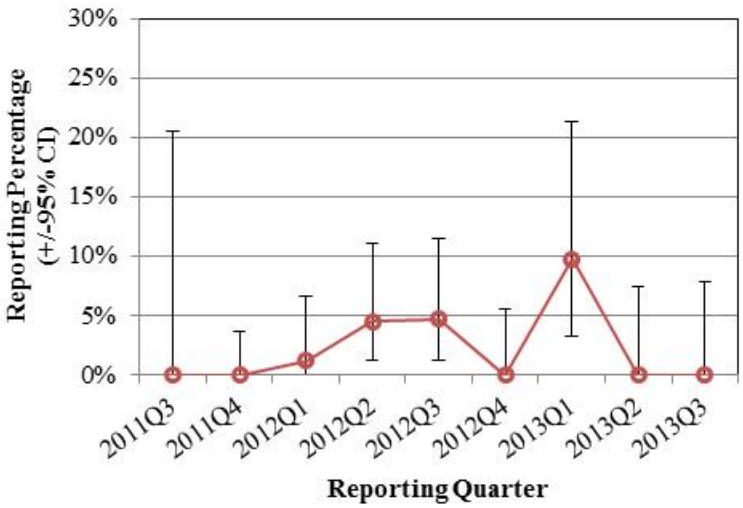

Figure 5: Reporting Percentage of US tapentadol ER Cases in SCEPTRE by Reporting Quarter – Overdose.

3.1.2.2.4.5.6. Trend Analysis – Decreased Potency

Figure 6 displays the reporting percentage by reporting quarter for decreased potency. Since US product launch, there have been 130 cases that reported decreased potency. The reporting percentage was relatively stable at 20-30% in the first 6 quarters after launch, increased to 41% in 2013Q1, decreased in 2013Q2 and increased again to 38% in 2013Q3. The overall pattern is indeterminate.

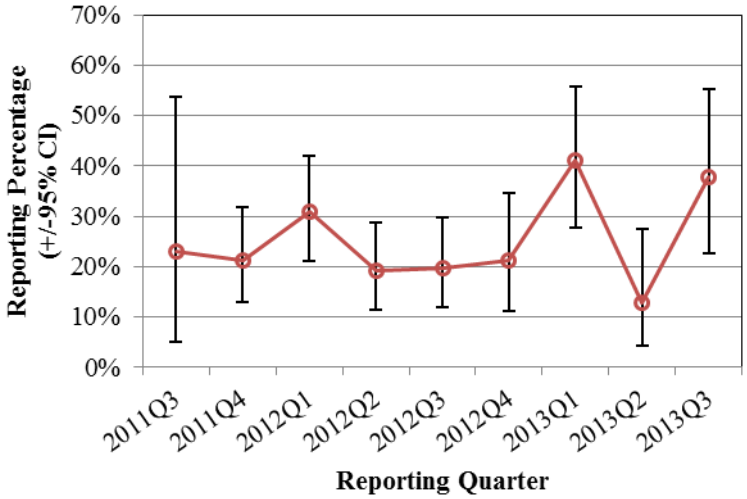

Figure 6: Reporting Percentage of US Tapentadol ER Cases in SCEPTRE by Reporting Quarter - Decreased Potency.

The 40 cases reporting Decreased Potency during the first three quarters of 2013 were reviewed. The cases generally contained very little information about the event. There was not overrepresentation of any reporting region (9 cases were from Florida, 4 from Pennsylvania, and the remaining cases were from 17 states), or lot number (only 4 cases contained batch/lot numbers). Twenty two of the 40 cases contained dosing information: in 17 the dosing appeared to be consistent with that described in the NUCYNTA USPI; in 5 the dose was low and there was no attempt made to titrate up. Three cases described a lack of effect during the change from NUCYNTA IR to NUCYNTA ER, and 6 cases did not indicate the lack of effect was related to NUCYNTA ER (eg lack of effect with another drug, lack of effect when a dose was missed). Overall these cases do not point to any particular cause of the decreased efficacy and do not represent a new signal.

3.1.2.2.4.5.7. Trend Analysis – Increased Potency

Figure 7 displays the reporting percentage by reporting quarter for increased potency. Since US product launch, there have been 7 cases that reported increased potency. The reporting percentage for increased potency was zero to 5% in all 9 quarters since launch; the overall pattern is stable.

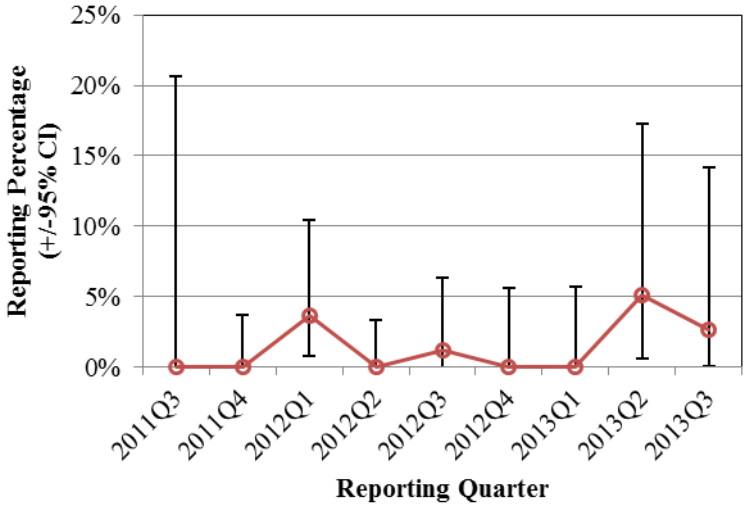

Figure 7: Reporting Percentage of US Tapentadol ER Cases in SCEPTRE by Reporting Quarter – Increased Potency

3.1.2.2.4.5.8. Trend Analysis – Respiratory Depression

Figure 8 displays the reporting percentage by reporting quarter for respiratory depression. Since US product launch, there have been 5 cases that reported respiratory depression. The reporting percentage was 8% in the first quarter (this represented 1 case) and has been zero or 1% over next 8 quarters. The reporting trend for respiratory depression is stable.

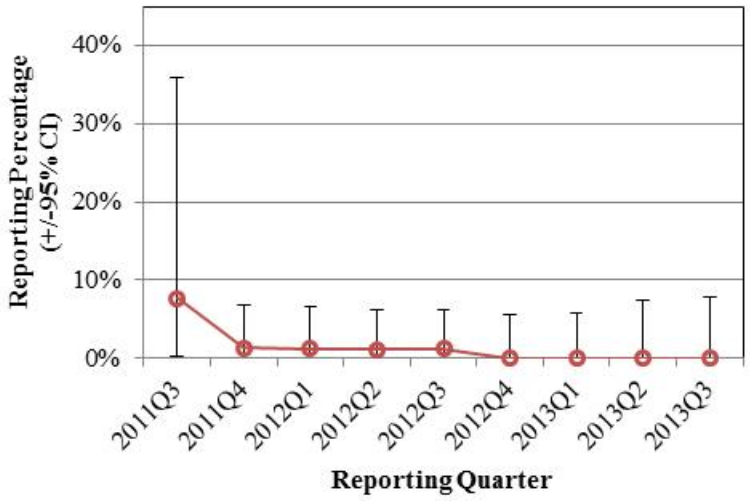

Figure 8: Reporting Percentage of US Tapentadol ER Cases in SCEPTRE by Reporting Quarter – Respiratory Depression.

3.1.2.2.4.5.9. Trend Analysis – Seizures

Figure 9 displays the reporting percentage by reporting quarter for seizure. Since US product launch, there have been 7 cases that reported seizure. The reporting percentage for seizures was or zero to 3% in all 9 quarters after launch; the overall pattern is stable.

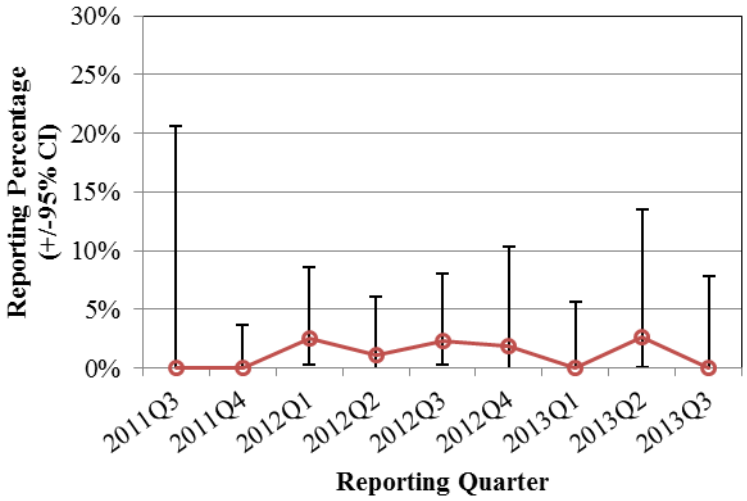

Figure 9: Reporting Percentage of US Tapentadol ER Cases in SCEPTRE by Reporting Quarter – Seizures.

3.1.2.2.4.5.10. Trend Analysis – Serotonin Syndrome

Figure 10 displays the reporting percentage by reporting quarter for serotonin syndrome. Since US product launch, there have been 21 cases that reported serotonin syndrome. The reporting percentage for serotonin syndrome has been zero to 8% each quarter; the reporting trend is indeterminate.

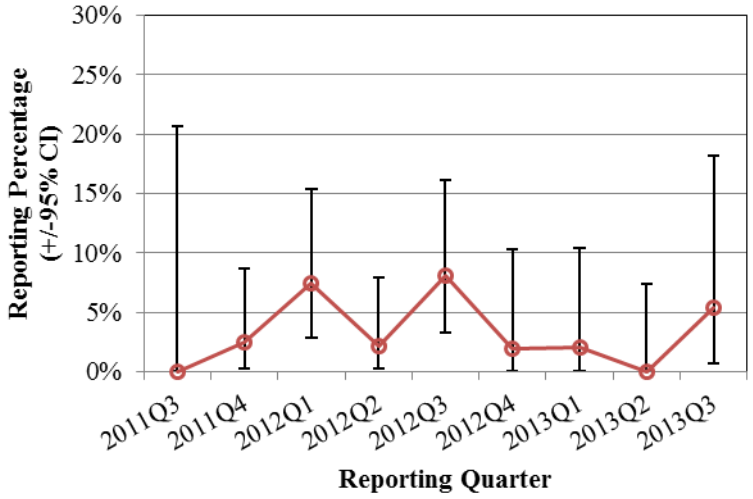

Figure 10: Reporting Percentage of Tapentadol ER Cases in SCEPTRE by Reporting Quarter - Serotonin Syndrome.

3.1.3. Summary of all Surveillance Conclusions

3.1.3.1. Conclusions for Routine Surveillance Activities

1. Intra-product signaling review and lot alert reviews for the period 01 January 2013 to 30 Jun 2013 identified no new validated signals requiring evaluation.

2. The data mining review of the FDA AERS 2012Q3 configuration identified no validated signals requiring further evaluation.

3.1.3.2. Conclusions for Product-Specific Surveillance Activities

Case Counts and Demographics for Events of Interest

1. The most frequently reported event of interest in SCEPTRE for tapentadol ER in the US is decreased potency. Medication errors, serotonin syndrome, and overdose are the next most frequently reported events of interest reported cumulatively in SCEPTRE. The remaining events of interest have been reported in US cases for tapentadol ER seven or fewer times cumulatively. During the current progress report period, the most frequently reported event of interest is medication errors.

   There are 118 total US cases in the most recent configuration (cumulative to 2012Q4) of the FDA AERS database reporting any adverse event with tapentadol ER; this number has slowly

increased through quarters 2011Q4 through 2012Q2 and decreased in 2012Q3 and 2012Q4. While the low number of cases reported for each event of interest within the FDA AERS database for tapentadol ER limits analyses, it can be noted that serotonin syndrome and decreased potency account for the largest number of spontaneous US cases reported within FDA AERS.

2. The most commonly reported age group in SCEPTRE for the US cases reporting events of interest with tapentadol ER is the 41 to 65 year-old age group. During the current report period, there were no pediatric or pregnancy cases in SCEPTRE.

   The most commonly reported age group for spontaneous US cases reporting any adverse event with tapentadol ER in the FDA AERS database is the 41 to 65 year-old age group. The FDA AERS database contains no cases reporting use of tapentadol ER in a patient less than 18 years old.

3. The most frequently reported sex in SCEPTRE for spontaneous tapentadol ER US cases reporting any adverse event, as well as most of the events of interest, is female. Serotonin syndrome was reported slightly more often in males than females. A number of other events of interest are reported more often in males; however the total number of these events is small.

   The most frequently reported sex in spontaneous US cases reporting any adverse event with tapentadol in the FDA AERS database is female. Serotonin syndrome was also reported more often in males than females.

Analysis of Cases

1. During the current progress report period, there were no initial US spontaneous cases reporting events suggestive of choking, sticking, and esophageal obstruction.

2. During the current progress report period, there were no initial US spontaneous case reporting use of tapentadol ER in the pediatric population

3. During the current progress report period, there were no initial US spontaneous cases reporting use of tapentadol ER during pregnancy and lactation.

4. There was 1 spontaneous case in SCEPTRE reporting seizures with the use of tapentadol ER received during the current progress report period. The case contained insufficient information for assessment against the current US label for tapentadol ER. Review of this case did not suggest a new safety concern.

5. Of the 3 spontaneous cases in SCEPTRE reporting serotonin syndrome with the use of tapentadol ER that were received during the current progress report period, only 1 contained sufficient information. The information provided was consistent in nature, severity, and outcome with the current US label for the product. Review of this case did not suggest a new safety concern.

SCEPTRE Reporting Trends

1. The low number of cases in SCEPTRE for the events of accidental exposure, addiction, diversion, drug abuse/intentional misuse, pediatric cases, and cases reporting pregnancy and lactation during this progress report period did not support an analysis of their reporting trends.

2. Reporting trends in SCEPTRE for choking, cases with fatal outcome, increased potency, respiratory depression, and seizures were stable.

3. Reporting trends in SCEPTRE for off-label use, overdose, decreased potency, and serotonin syndrome are indeterminate.

Case level review of decreased potency cases did not indicate any cause of the events and did not indicate that this event represents a signal.

4. Reporting percentage was greatly increased in 2013Q1, 2013Q2, and 2013Q3 compared with all previous quarters for medication errors. This increase is consistent with a recent change in case processing conventions. Case level review did not indicate any unusual patterns representing a signal. The reporting of this event will continue to be monitored during intra-product signaling reviews.

3.1.4. Product-Specific Surveillance Activities Involving External Databases (RADARS® System Programs)

Janssen Scientific Affairs (JSA) receives information quarterly from the RADARS® System. The RADARS® System uses active surveillance methods to collect, compile, analyze, and maintain certain de-identified health care and other information in proprietary databases in an effort to monitor for misuse, abuse, and diversion (whether intentional or unintentional) by patients, health care practitioners, or other individuals. The RADARS® System contains data from 6 programs, 5 of which JSA receives data from: an opioid treatment program network, a drug diversion network, a key informant network, a poison center network, and a college survey program. Information regarding tapentadol ER and other target drugs, including oxycodone, hydrocodone, morphine, hydromorphone, fentanyl, buprenorphine, methadone, and tramadol, is reported to JSA as rates per 3-digit ZIP code, in an effort to measure geographic specificity per drug, per RADARS® System Program. All RADARS® System Programs reported rates are calculated as per 100,000 population and per 1,000 unique recipients of dispensed drug (URDD). URDD is the number of unique individuals filling a prescription in a given 3-digit ZIP code, accounting for prescription refills. For example, if during one quarter a person filled a prescription several times, they would be counted as a single URDD.

Descriptions of the methodology of each of the RADARS® System Programs are presented below.

3.1.4.1. Opioid Treatment Program Network

The American Association for the Treatment of Opioid Dependence (AATOD) and the National Development and Research Institutes (NDRI) are working collaboratively to determine the prevalence of prescription opioid abuse among admissions to opioid treatment programs (OTPs) nationally, including methadone maintenance programs, and focus on the states with the highest risk.

3.1.4.1.1. Objectives

The objectives of this Program are:

- To estimate the point (1 month) and lifetime prevalence of prescription and illicit opioid abuse in a national sample of patients enrolling in methadone maintenance treatment programs (MMTPs).
- To determine the primary drug (in relation to opioids used) among methadone maintenance treatment program enrollees.

3.1.4.1.2. Methods

Patients enrolling in 1 of the participating MMTPs are voluntarily recruited within the first week of admission and complete a self-administered questionnaire. The questionnaire consists of basic demographics, ZIP code of patient's residence, opioid drug use (past month, lifetime, and age of first), primary drug of abuse, source for primary drug, drug craving, drug withdrawal, and several questions related to pain. Between 01 January 2005 and 30 June 2013, a total of 56,369 patients from 75 MMTPs throughout the US had completed the questionnaire. The completed questionnaires are faxed to NDRI on a designated day of the week.

3.1.4.1.3. Summary of Results

- **National Level Data**

The opioid abuse rates on a population basis and URDD basis over time estimated from the selected national sample of patients enrolling in methadone maintenance treatment for all RADARS® System opioids are represented graphically in Figure 11 and Figure 12, respectively. For the reporting periods of 2012Q4, 2013Q1, and 2013Q2, the past 30 day endorsement rates for tapentadol in the OTP program were 0.0403, 0.0389, and 0.0422, respectively per 100,000 population, and 0.5799, 0.8574, and 0.9646, respectively per 1,000 URDD.

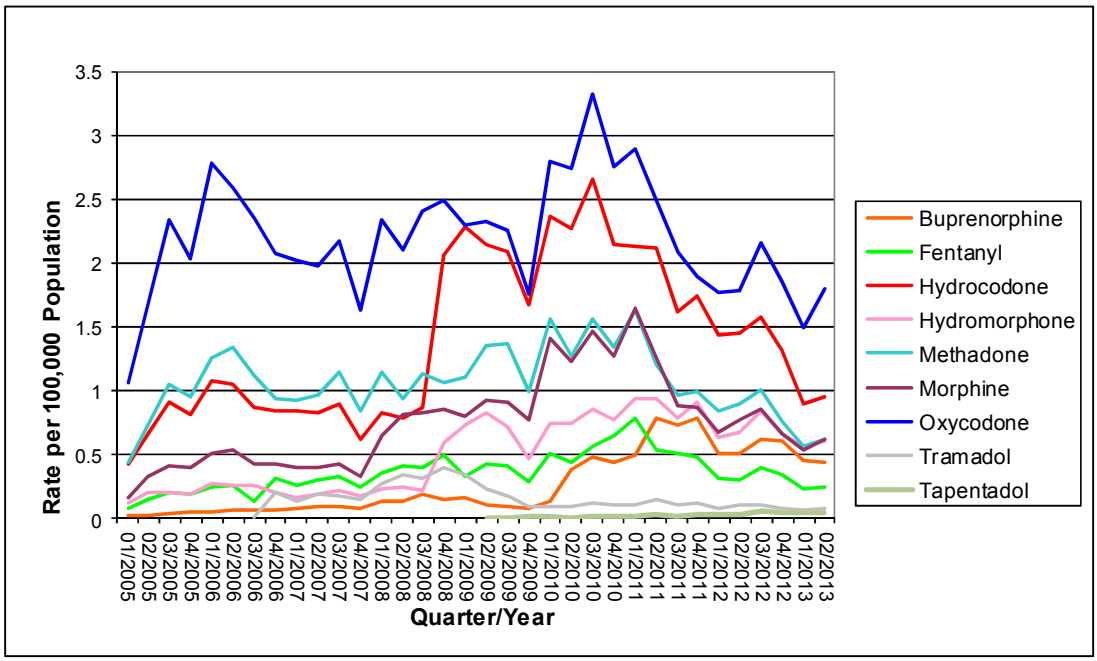

Figure 11: Opioid Treatment Program Abuse Rates At A National Level (per 100,000 Population) by Quarter

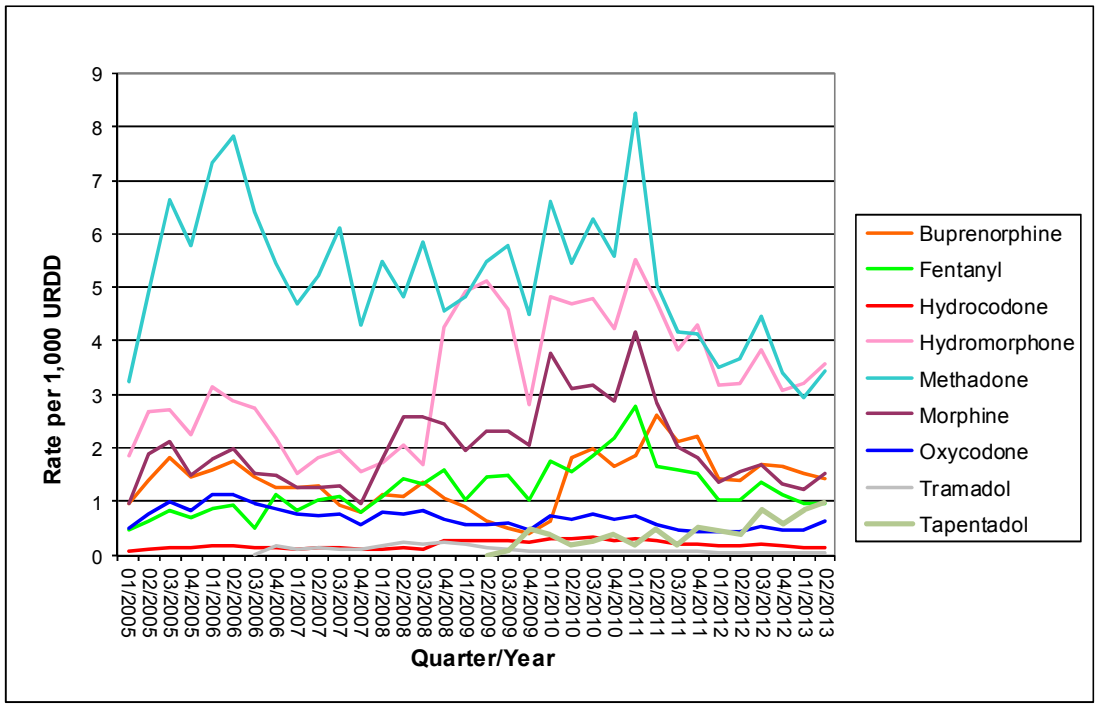

Figure 12: Opioid Treatment Program Abuse Rates (per 1,000 URDD) Over Time – Target Drugs

3.1.4.2. Drug Diversion Program

This program is conducted by the Center for Applied Research on Substance Use and Health Disparities at Nova Southeastern University to determine the rates of diversion of selected prescription opioids based on case information obtained from a nationwide sample of police and regulatory agencies.

3.1.4.2.1. Objectives

- To determine the rates of diversion of selected prescription opioids in a nationwide sample of police and regulatory agencies.
- To calculate rates of diversion per 100,000 population and per URDD.

3.1.4.2.2. Methods

At the beginning of each quarter, the diversion survey participants are sent a survey that requests the total number of new cases of pharmaceutical diversion reported to and/or investigated by the diversion unit during the previous 3 months. For each of the drugs monitored by the RADARS® System, the number of cases and the dosage form is also requested.

As of April 2013, the study sample for 2013Q2 included 250 diversion investigators from all 50 states, including rural, suburban, and urban areas. Of the 250 sites currently participating in the survey, 45% are municipal police departments, 27% are multi-jurisdictional drug task forces, 19% are county sheriffs' departments, 4% are regulatory agencies such as medical and pharmacy boards, and the remaining 5% include state police agencies, prosecutors' offices, and departments of health.

3.1.4.2.3. Summary of Results

- **National Level Data**

The Drug Diversion rates on a population basis and URDD basis over time are represented graphically and shown in Figure 13 and Figure 14, respectively, for all RADARS® System Opioids. For the reporting periods of 2012Q4, 2013Q1, and 2013Q2, the Drug Diversion rates for tapentadol were 0.0058, 0.0034, and 0.0042, respectively per 100,000 population, and 0.0747, 0.0691, and 0.0881, respectively per 1,000 URDD.

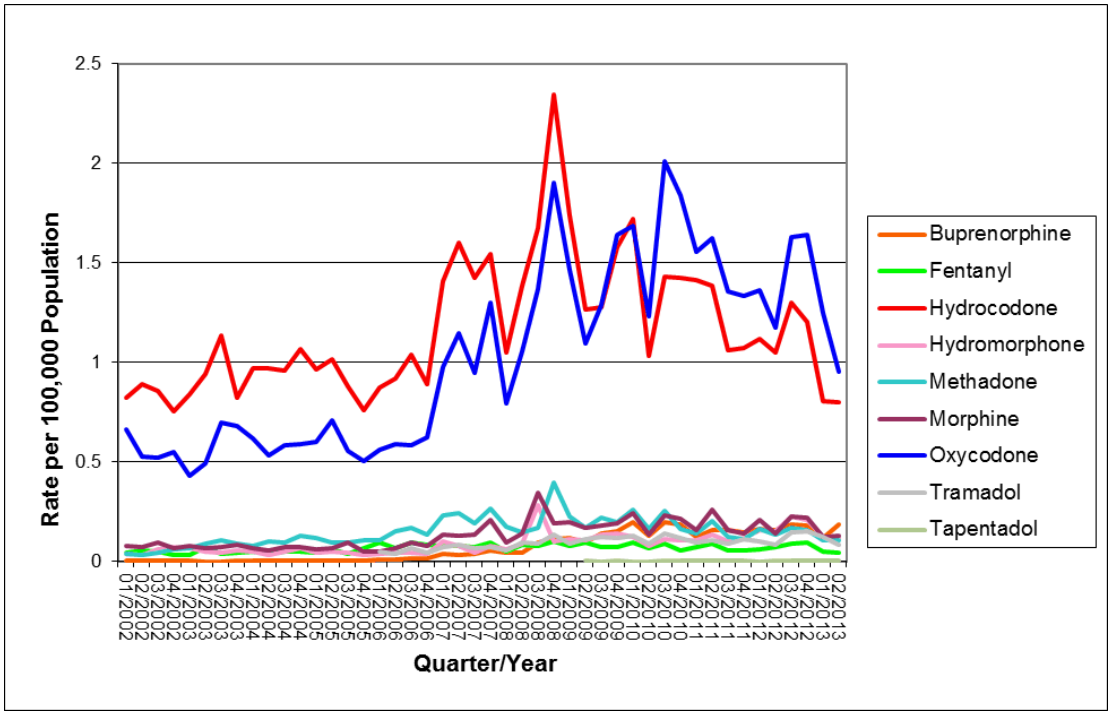

Figure 13: Drug Diversion Rates At A National Level (per 100,000 Population) by Quarter – all RADARS® System Opioids

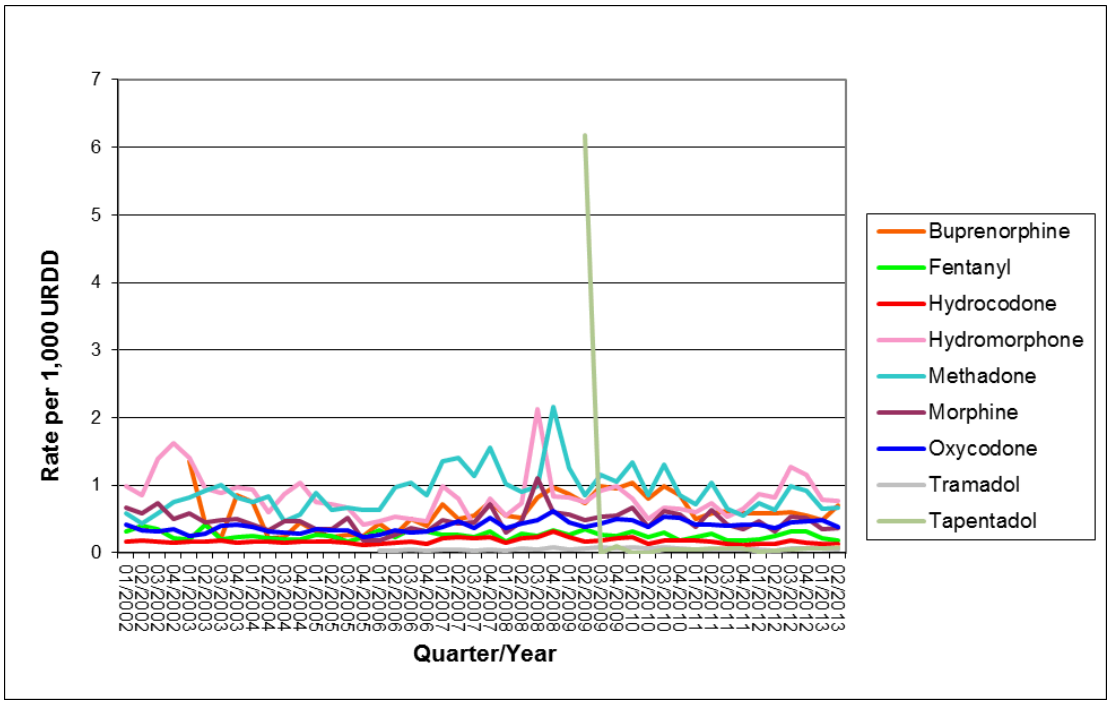

Figure 14: Drug Diversion Rates (per 1,000 URDD) Over Time – all RADARS® System Opioids

3.1.4.3. Survey of Key Informants' Patients Program

This program is conducted through the Washington University (WU) School of Medicine to ascertain the number of people nationwide who might be abusing specific opioids and to describe the general characteristics of the abuse patterns.

3.1.4.3.1. Objectives

- To proactively seek evidence of abuse in individuals at risk for abuse of prescription drugs across the US based on a survey of Key Informants' (KIs) patients.

3.1.4.3.2. Methods

Washington University mails hard copies of questionnaires to the KIs who have opted to enlist their patients to complete the Patient Questionnaires. Blank questionnaires are mailed to the KIs (in batches of 10) along with patient incentives and self-addressed stamped envelopes, to allow the patient to complete the questionnaire independently without the KI's evaluation and submit it to WU. All questionnaires are tracked indicating sent and received date.

The key informant network is comprised of individuals drawn from the following sources: National Institute on Drug Abuse (NIDA) grantees that monitor substance abuse, drug abuse treatment centers, pain clinics and pain specialists, State Impaired Health Care Professionals, and methadone specialists. These individuals are experts in the field of substance abuse and pain medicine and are in the position to evaluate, treat or otherwise know about new and emerging drug problems in their communities.

In the fourth quarter of 2012, 704 of 833 (84.5%) questionnaires were completed and returned. There were 159 KIs from 49 states that have agreed to enlist their patients who claim any use of prescription opiates to complete an anonymous patient questionnaire.

In the first quarter of 2013, 756 of 1,047 (72.2%) questionnaires were completed and returned. There were 173 KIs from 50 states that have agreed to enlist their patients who claim any use of prescription opiates to complete an anonymous patient questionnaire.

In the second quarter of 2013, 801 of 1,043 (76.8%) questionnaires were completed and returned. There were 176 KIs from 48 states that have agreed to enlist their patients who claim any use of prescription opiates to complete an anonymous patient questionnaire.

3.1.4.3.3. Summary of Results

- **National Level Data**

The rates of abuse over time from the Survey of Key Informants' Patients (SKIP) program on a population basis and a URDD basis are shown graphically in Figure 15 and Figure 16, respectively. For the reporting periods of 2012Q4, 2013Q1, and 2013Q2, the past 30 day endorsement rates for tapentadol in the SKIP program were 0.0253, 0.0159, and 0.0074, respectively per 100,000 population, and 0.3741, 0.3245, and 0.1668, respectively per 1,000 URDD.

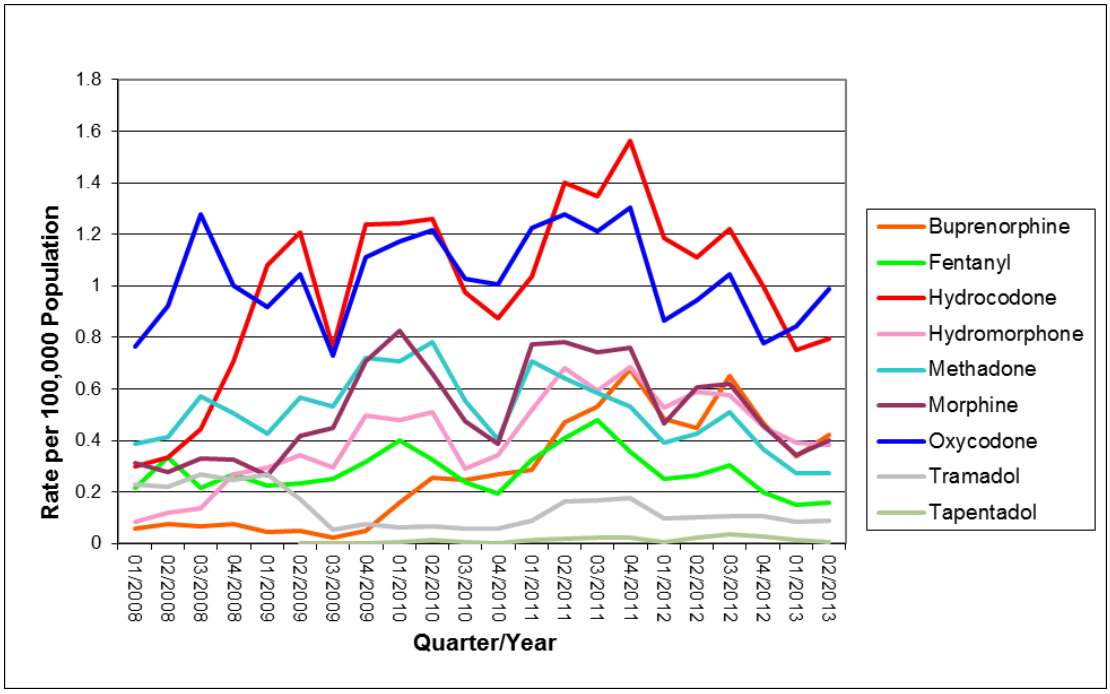

Figure 15: Survey of Key Informants' Patients Abuse Rates (per 100,000 Population) Over Time – All RADARS® System Opioids

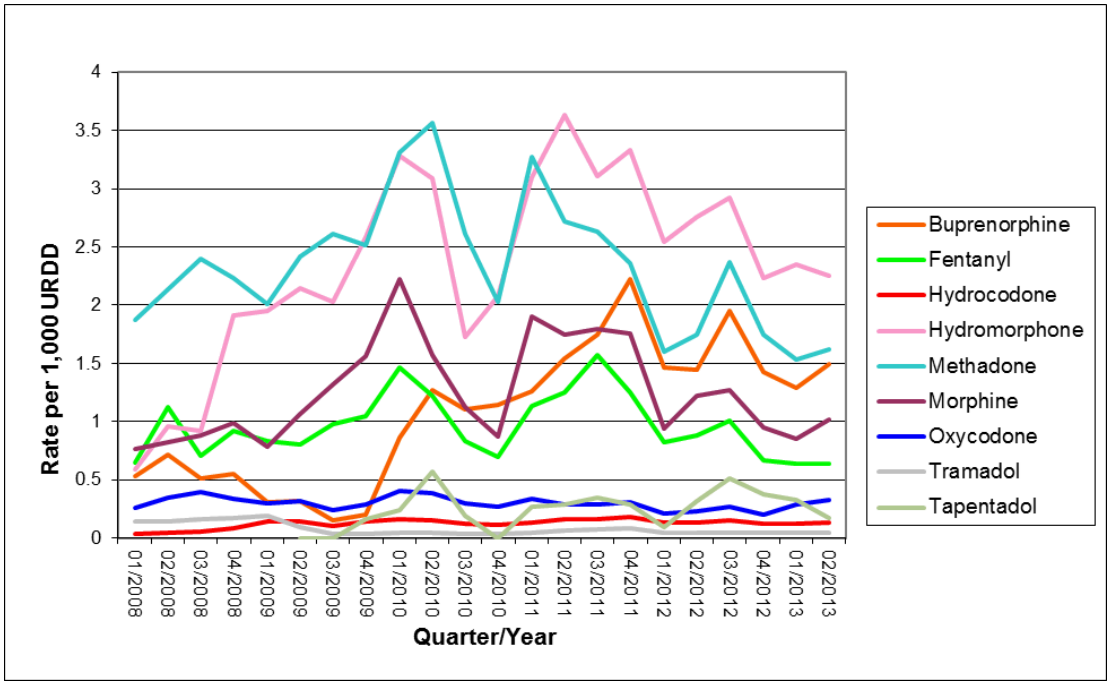

Figure 16: Survey of Key Informants' Patients Abuse Rates (per 1,000 URDD) Over Time – all RADARS® System Opioids

3.1.4.4. Poison Center Network

This program is conducted at the Rocky Mountain Poison and Drug Center (RMPDC) to compile information concerning targeted prescription pain medications associated with cases reported to the center and at least 40 other regional poison centers.

3.1.4.4.1. Objectives

- The objective of the Poison Center Network is to identify all exposure cases involving target prescription pain medications reported to the RMPDC and other regional poison centers.

3.1.4.4.2. Methods

Investigators at a participating regional poison center use a standardized, pre-formatted database to extract all exposure and information cases regarding JSA target drugs, which include tapentadol ER, oxycodone, hydrocodone, morphine, hydromorphone, fentanyl, buprenorphine, methadone, and tramadol. After removing all patient identifiers, the cases are emailed to RMPDC on a weekly basis. The cases are divided into 2 categories: unintentional/other exposures and intentional exposures. The criteria for classifying a case as an intentional exposure include suspected suicide, intentional misuse, abuse, intentional unknown, and withdrawal cases. This category is used as a surrogate for misuse and abuse. The unintentional/other exposures category includes cases resulting from

unforeseen or unplanned events, adverse reactions, and other unknown reasons.

3.1.4.4.3. Summary of Results

- **National Level Data**

The national level Poison Center intentional exposure rates over time for all RADARS® System Opioids are represented graphically in Figure 17 and Figure 18, for population and URDD, respectively. For the reporting periods of 2012Q4, 2013Q1, and 2013Q2, the intentional exposure mention rates for tapentadol in the Poison Center program were 0.0163, 0.0156, and 0.0088, respectively per 100,000 population, and 0.2392, 0.3322, and 0.1993, respectively per 1,000 URDD.

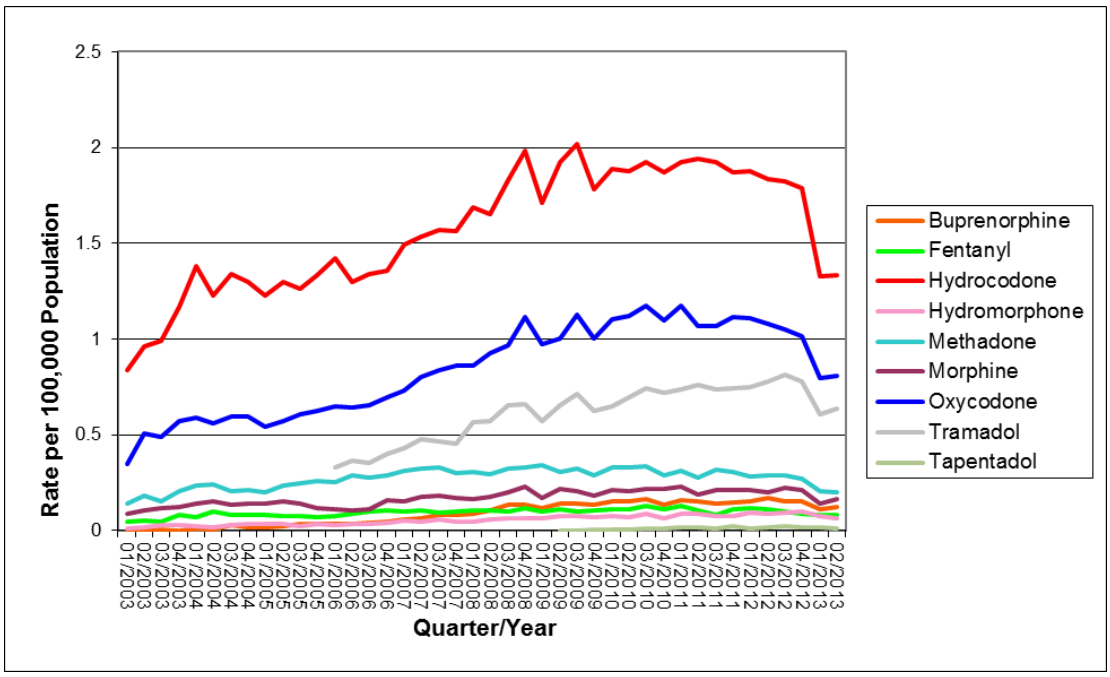

Figure 17: Poison Center Intentional Exposure Rates (per 100,000 population) by Quarter

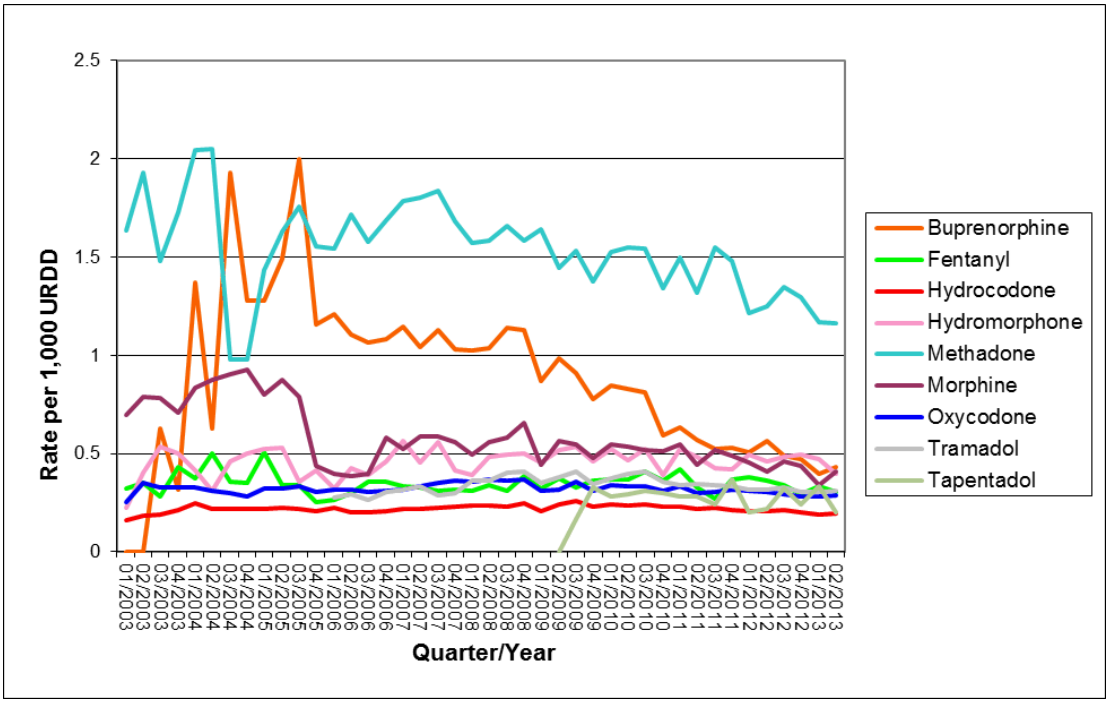

Figure 18: Poison Center Intentional Exposure Rates (per 1,000 URDD) by Quarter

- **Poison Center: Intentional and Unintentional Exposure**

Patient characteristics and demographics of tapentadol ER intentional and unintentional exposures for the reporting periods of 2012Q4, 2013Q1, and 2013Q2 are presented in Table 12 and Table 13:

Table 12: Poison Center Patient Demographics and Outcome of Tapentadol ER Intentional Exposures

	2012Q4	2013Q1	2013Q2
TOTAL	**24**	**28**	**18**
Gender			
Male	6	8	4
Female	18	20	14
Unknown	0	0	0
# of Drugs Involved			
Single	7	8	10
Multiple	17	20	8
Outcome			
No effect	2	5	2
Minor	8	7	8
Moderate	10	12	6
Major	1	1	1
Death	0	0	0
Death, indirect	0	0	0
No follow-up**	3	2	1
Unrelated effect	0	1	0
Confirmed non-exposure	0	0	0
Missing	0	0	0

Key: ER=Extended-release; Q=Quarter
** No follow-up, non-toxic, minimally toxic, potentially toxic

Table 13: Poison Center Intentional and Unintentional/Other Exposures by Age Group (Years)

	2012Q4		2013Q1		2013Q2	
	IE	UE	IE	UE	IE	UE
TOTAL	**24**	**44**	**28**	**23**	**18**	**22**
Age						
0-5	0	4	0	2	0	5
6-12	0	0	0	0	0	0
13-19	1	0	3	1	3	0
20-29	3	2	4	0	4	0
30-39	2	12	6	5	3	6
40-49	10	4	7	5	3	2
50-59	5	5	2	4	2	2
60-69	2	8	3	2	2	5
70-79	0	2	0	2	1	0
80-89	0	1	1	1	0	0
≥90	0	0	0	0	0	0
Unknown	1	6	2	1	0	2

Key: IE=Intentional exposure; Q=Quarter; UE=Unintentional/other exposure

In 2012Q4, there were 24 cases of intentional exposure to ER tapentadol. There were 4 cases of unintentional/other exposures for ages 0 to 5 years and 6 to 12 years.

In 2013Q1, there were 28 cases of intentional exposure to ER tapentadol. There were 2 cases of unintentional/other exposures for ages 0 to 5 years and 6 to 12 years.

In 2013Q2, there were 18 cases of intentional exposure to ER tapentadol. There were 5 cases of unintentional/other exposures for ages 0 to 5 years and 6 to 12 years.

3.1.4.5. College Survey Program

The RADARS® System College Survey program is an online questionnaire, which collects data from self-identified college students attending a two- or four-year college, university, or technical school at least part-time during the specified sampling period. Data are collected at the completion of the fall and spring academic semesters/quarters and at the end of the summer.

3.1.4.5.1. Objectives

- To estimate the scope of prescription drug use for nonmedical reasons among college students in the United States.
- To determine the route of administration respondents chose to use their drugs.
- To determine the source from which respondents obtain their drugs.

3.1.4.5.2. Methods

The sample is obtained through the use of a survey panel company in which respondents voluntarily register. The sample is equally distributed across the 4 geographic regions of the United States (W, NW, S, and NE). Each launch of the questionnaire collects responses from approximately 2,000 college students. Data are collected at the completion of the fall semester (during the second two weeks of December), at the completion of the spring semester (during the second two weeks of May), and at the completion of the summer (during the first two weeks of August). Rates are calculated as per 100,000 population and per 1,000 URDD.

- Design of the Questionnaire

Respondents complete an online questionnaire designed to be self-administered. The questionnaire consists of basic demographic items (including age, sex, race, and Hispanic origin), 3-digit ZIP code where respondent reports living during the specified sampling period, grade point average, prescription drug use (including opioids, stimulants, and carisoprodol), source from which drug was obtained, and route of administration.

3.1.4.5.3. Summary of Results

- **National Level Data**

The opioid abuse rates in the College Survey Program for all RADARS® System opioids on a population and URDD basis over time through 2013Q1 are estimated from the national sample of respondents submitting valid College Survey questionnaires and are represented graphically in Figure 19 and Figure 20, respectively. The College Survey was not administered in 2013Q2.

For the reporting periods of 2012Q4 and 2013Q1 the past 3 month nonmedical use rates for tapentadol were 0.0134 and 0.0079, respectively per 100,000 population, and 0.1894 and 0.1650, respectively per 1,000 URDD.

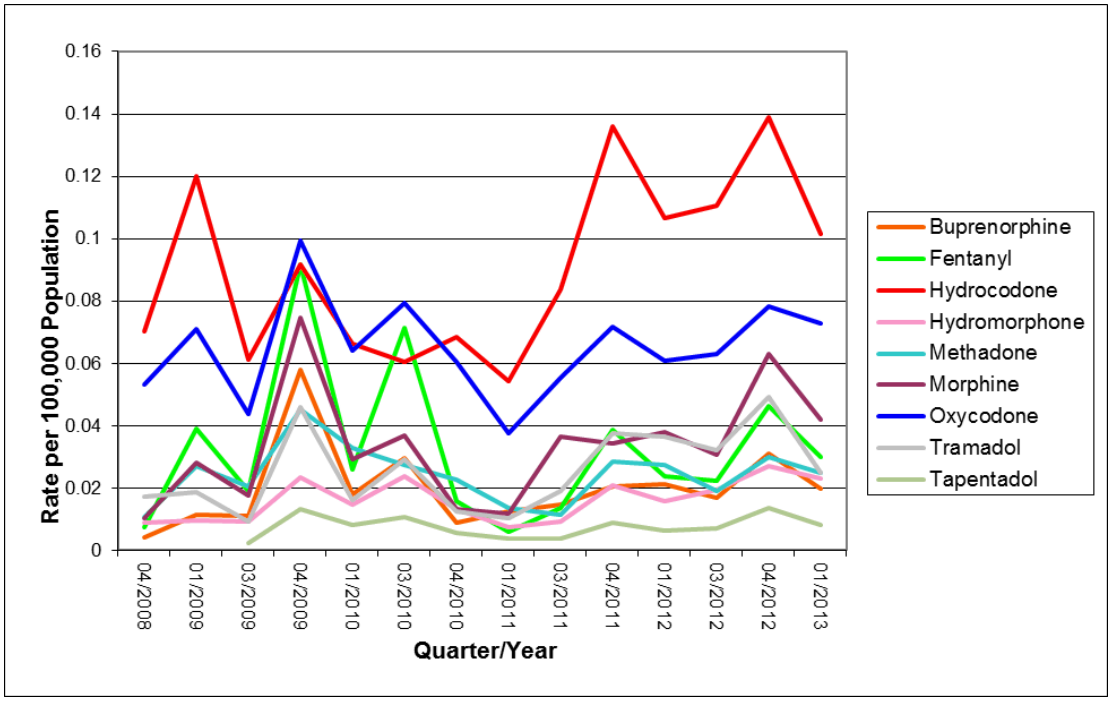

Figure 19: College Survey Abuse Rates (per 100,000 Population) Over Time – all RADARS® System Opioids

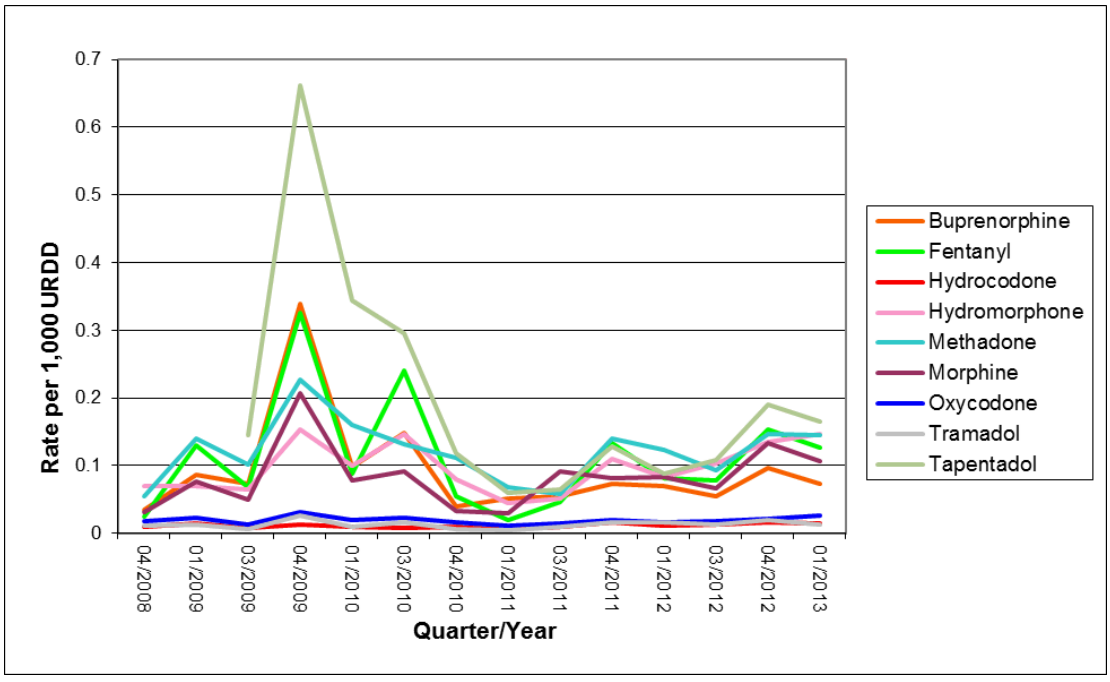

Figure 20: College Survey Abuse Rates (per 1,000 URDD) Over Time – all RADARS® System Opioids

3.1.4.6. Summary of Findings from All RADARS® Programs

Overall Summary

On the population basis, rates of abuse, misuse, and diversion of tapentadol ER were the lowest of the RADARS opioids. The estimated trend in Drug Diversion tapentadol ER population rates through 2013Q2 showed a non-significant increase over time. However, the estimated trend in SKIP, OTP, and Poison Center population rates through 2013Q2 showed a non-significant decrease over time. The estimated trend in College Survey tapentadol ER population rates through 2013Q1 showed a non-significant increase over time.

On an URDD basis, rates of abuse, misuse, and diversion of tapentadol ER were among the lowest of the RADARS opioids. The estimated trend in Drug Diversion and OTP tapentadol ER URDD rates through 2013Q2 showed a non-significant increase over time. However, the estimated trend in SKIP and Poison Center population rates through 2013Q2 showed a non-significant decrease over time.

Although the number of mentions remains low, the estimated trend in College Survey tapentadol ER URDD rates through 2013Q1 showed a significant increase. To understand whether it represents a trend, an additional several quarters of data are required. As such, the significance of these findings is unclear at this time. Continued monitoring is required.

Population data in the Poison Center shows that tapentadol had the fewest number of intentional exposures, and is among the lowest tertile of all 9 comparators by URDD.

Conclusion

Based on the RADARS® data presented, the findings suggest that current rates of abuse and diversion of tapentadol are low; however, continued monitoring of trends is warranted.

3.1.5. Product –Specific Surveillance Activities Involving External Databases (NAVIPPRO® System Programs)

The NAVIPPRO® system provides reports to Janssen Scientific Affairs over a 4-month period, with a 2-month lag time following each period for report preparation. The current report contains data for Period 1 (01 January 2013-30 April 2013) (P1 2013).

NAVIPPRO® is a national program that includes surveillance as well as prevention and intervention educational programs for substance abuse. NAVIPPRO® surveillance involves analyses from 3 data sources: Addiction Survey Index Multimedia Version (ASI-MV®), Comprehensive Health Assessment for Teens (CHAT®), and Web Informed Services (WIS®) Internet Monitoring Archive for indicators of prescription opioid medication abuse. Information regarding NUCYNTA® ER and other target drugs, including oxymorphone ER, oxycodone ER, hydromorphone ER, and tramadol ER is reported to JSA. The various data sources are intended to complement each other; an indication of increased abuse of a particular product found in one data source can be examined and evaluated with other sources within NAVIPPRO®. Continuous examination of these data streams allows monitoring of trends over time for drug abuse at a product-specific level.

In this report, analysis of ASI-MV® and CHAT® data is presented primarily for NUCYNTA® ER. Analysis of Internet monitoring data, however, is presented for all tapentadol-related Internet discussions regardless of the formulation.

3.1.5.1. Addiction Survey Index Multimedia Version (ASI-MV®)

3.1.5.1.1. Objectives

The Addiction Severity Index (ASI) is a standard tool used in the assessment of substance abuse and several psychosocial problem areas typically associated with substance use including: medical, employment, psychiatric, and legal status, as well as family and social functioning. It is traditionally administered by clinicians in a treatment setting upon intake for substance abuse treatment to adults, aged 17 years and older (although some sites administer the ASI to children as young as 14 years of age).

The ASI-MV® is a computer-administered version of the ASI that, in addition to the core traditional ASI questions, contains questions about abuse of prescription medications, including information on the route of administration and the source of the prescription medication at a product-specific level. Respondents are presented with the names of prescription medications and other drug products as well as pictures to help distinguish exactly which products they used. The ASI-MV® assessment gathers self-reported data in near real time on respondents from a network of

facilities across the United States. These facilities utilize the assessment for treatment planning and triage in relation to substance abuse problems.

3.1.5.1.2. Methods

- **Dataset**

The ASI-MV® data are provided from sites that use the system for their client assessments. A varying number of sites per state are active in a reporting period, and varying numbers of sites complete data transfers to the NAVIPPRO® data center per reporting period. The dataset is used to monitor trends among this sentinel sample of individuals who are considered at high risk of abusing prescription medications. National rates of abuse are not reported since the dataset is not a nationally representative sample.

- **Definition of Abuse**

Abuse of a prescription medication is captured via self-report during the ASI-MV® computer-administered interview. Past 30-day abuse was defined as any strictly non-medical use of a prescription opioid medication. To determine whether use of each prescription opioid medication an individual had endorsed was legitimate for treatment of pain, a series of questions within the ASI-MV® established that the individual had:

  - a current pain problem and had taken a prescribed opioid medication for pain in the past 30 days
  - obtained the medication only from their own prescription; and had not used the medication via an alternative route of administration
  - not used a prescription opioid medication in the past 30 days in a way not prescribed by their doctor, that is, for the way it makes them feel and not for pain relief

An algorithm based on the responses to these questions classified individuals as having engaged in non-medical use (and therefore abuse) or, under the conditions specified above, classified individuals as "use as prescribed."

- **Rates of Prescription Opioid Abuse Calculation**

Rates of abuse and 95% confidence intervals of target and comparator products were examined for the reporting period. Rates of abuse for each product were calculated as:

- Number of abuse cases per 100 ASI-MV® assessments; denominator = all ASI-MV® assessments from the network of ASI-MV® sites tracking NUCYNTA® ER in the dataset for the reporting period
- Number of abuse cases per 100 prescription opioid abusers assessed; denominator=all prescription opioid abusers from the network of ASI-MV® sites tracking NUCYNTA® ER in the dataset for the reporting period
- Number of abuse cases per 100,000 prescriptions dispenses; denominator = total prescriptions dispenses for the target and comparators during the reporting period

The numerator for each rate of abuse calculation is any past 30-day abuse of the target or comparator products reported in the dataset for the reporting period of P1 2013. The confidence intervals for each rate are calculated at the 95% confidence level and when appropriate (i.e., when the numerator, n, is less than 30) with use of a Poisson distribution. Statistical significance was defined as non-overlapping 95% confidence intervals.

To calculate rates of abuse on the basis of prescription availability (i.e., per 100,000 prescriptions dispensed), the prescription volume data include only prescriptions dispensed in states with sites that contributed assessments to the ASI-MV® network during the reporting period, to provide a more accurate estimate of the potential availability of products in the areas monitored. Prescription volume data are obtained from a commercial vendor, IMS Health (formally SDI Health), for the reporting period. These data are derived from the Sub-National Pain Market Prescription Tracking database which includes data from a variety of sources, including pharmacies, payers, and switch houses. The prescription data sample comprises nearly 59,000 pharmacies (over 99% of retail stores) in the United States and includes cash, Medicaid, and third-party transactions. Data are representative of the retail pharmacy universe and do not include other potential channels of distribution, such as long-term care, hospital dispensaries, and mail order.

- **Prescription Opioid Abuse Data Analysis Based Upon Geographic Distribution**

The rate of abuse of any prescription opioid product is reported at the state level for the reporting period**.** The rate of abuse for each state is calculated by aggregating data from all of the state's ASI-MV® sites; rates of abuse are not presented for states with sites that contributed fewer than 10 assessments

collectively. For products with fewer than 30 total abuse cases, the distribution of cases by site is presented descriptively. ArcGIS (mapping and spatial analysis software; ESRI Inc.) is used to illustrate each site that contributed data as a geographic point on a map and to thematically illustrate rates of abuse by state.

- **Prescription Opioid Abuse Analysis Based Upon Demographics**
  - Demographic and abuse characteristics reported included respondent's age, sex, product-specific routes of administration, and sources of prescription medication**.** These data are used for stratified descriptive analysis. When product-specific data have a small sample size (i.e., when the denominator, n, is less than 30), the total case count is presented and percentages are not calculated, as these results are difficult to interpret.

3.1.5.1.3. Summary of Results

A total of 420 sites located in 34 states (including the District of Columbia) contributed data to the ASI-MV® network. Of these, 388 sites located in 33 states (including the District of Columbia), tracked the use and abuse of the ASI-MV® network prescription opioids, including NUCYNTA® ER. Collectively, these 388 sites contributed a total of 18,491 adult assessments to the ASI-MV® network. Nearly 61% of all assessments submitted to the ASI-MV® network from centers tracking NUCYNTA® ER were identified from the states of New Mexico, North Carolina, Missouri, Oklahoma, and Tennessee. The majority of individuals who indicated past 30-day abuse of any prescription opioid product was Caucasian (78.5 %), between 21 and 34 years of age (61.0%) and had never been married (56.6%); 50.6% were male. Prescription opioid abusers were also more likely to report having a chronic medical problem (40.3% versus 29.4%) as well as a self-reported pain problem (50.4% versus 33.1%) than the entire network. Only 35.7% of past 30-day prescription opioid abusers reported having been prompted by the criminal justice system to enter a treatment program, compared to 59.3% of all individuals in the ASI-MV® network.

- **Geographic Distribution of Abuse of NUCYNTA® ER**

No cases of past 30-day NUCYNTA® ER abuse were reported during P1 2013.

- **Demographic Analysis and Abuse Characteristics of NUCYNTA® ER and Comparators**

No cases of past 30-day abuse of NUCYNTA® ER were observed during P1 2013.

- **Rates of Abuse in the ASI-MV® Network: NUCYNTA® ER and comparators**

There was no rate of past 30-day abuse of NUCYNTA® ER, as no cases of past 30-day abuse were observed during P1 2013 (Table 14).

Table 14: Rates of Abuse for NUCYNTA® ER and Comparator Compounds Within the ASI-MV Network for P1 2013

	Total abuse cases	Rate per 100 assessments (n = 18,491)			Rate per 100 prescription opioid abusers assessed (n = 4,283)			Rate per 100,000 prescriptions dispensed		
	N	Rate	95% CI		Rate	95% CI		Rate	95% CI	
NUCYNTA® ER	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Original Oxymorphone ER (Quarterly average rate) †*	1,653	0.59	0.56	0.62	3.17	3.02	3.32	65.48	62.32	68.63
Original Oxymorphone ER (maximum quarterly rate) †*	338	1.95	1.74	2.15	9.28	8.34	10.22	116.68	104.25	129.11
Original Oxycodone ER (Quarterly average rate)†*	8,921	5.08	4.98	5.19	29.13	28.62	29.64	51.99	50.91	53.07
Original Oxycodone ER (maximum quarterly rate)†*	1,172	6.39	6.04	6.75	32.86	31.32	34.40	80.13	75.54	84.72
Hydromorphone ER	3	0.02	0.003	0.05	0.07	0.01	0.20	5.45	1.12	15.92
Tramadol ER	56	0.30	0.22	0.38	1.29	0.96	1.63	31.78	23.46	40.10

Key: ASI-MV=Addiction Severity Index Multimedia Version; CI=Confidence interval; ER=Extended release; P=Period; N/A=not applicable (as no cases of past 30-day abuse were observed during P1 2013)
*Baseline rates of abuse are presented for extended release oxycodone and extended release oxymorphone as a range (the quarterly average rate of abuse for the baseline period to the maximum quarterly rate observed). Note these variables were calculated using a different denominator than presented in this table.
†NOTE: Baseline Oxymorphone ER and Baseline Oxycodone ER refer to the original versions of each product prior to the introduction of the reformulated tablets in 2012 and 2010, respectively.

- **Overall Summary**

For Period 1 of 2013, of the 18,491 assessments submitted from the ASI-MV® network monitoring opioid abuse, including NUCYNTA® ER, 4,283 individuals (approximately 23% of all individuals assessed) reported past 30-day abuse of any prescription opioid product. No cases of past 30-day abuse of NUCYNTA® ER were observed.

3.1.5.2. Comprehensive Health Assessment for Teens (CHAT®)

3.1.5.2.1. Objectives

CHAT® is a computerized behavioral health assessment targeted for adolescents age 18 years of age and younger entering treatment for drug or alcohol abuse. Questions included in the assessment are related to adolescent experiences in 5 different domain areas: self and personality factors, family and peer relations, physical and emotional health, psychological issues, and drug use experiences. CHAT® was developed with support from the National Institutes of Health and the National Institute on Drug Abuse and has demonstrated validity and reliability as an assessment tool for adolescents in the treatment setting.

The CHAT® network of participating sites includes treatment centers and other facilities, such as alternative schools and mental health programs. The computerized assessment collects data on abuse of prescription medications at a product-specific level, including photographs of brand and generic medications and their street names, routes of administration, and source of the prescription medication. CHAT® monitors similar prescription medications tracked by the ASI-MV®.

3.1.5.2.2. Method

- **Dataset**

The CHAT® data are provided from sites that use the system for their adolescent assessments. A varying number of sites per state are active in a reporting period, and varying numbers of sites complete data transfers to the NAVIPPRO® data center per reporting period. The CHAT® network is expanding at this time. Consequently, the dataset has a small sample size.

- **Definition of Abuse**

Definitions of abuse are similar to the ASI-MV®.

- **Analyses**

CHAT® data are presented and summarized descriptively, given the small sample size.

3.1.5.2.3. Summary of Results

- **Summary of Participant Data**

For Period 1, a total of 90 sites, located in 15 states, contributed 1,399 assessments to the CHAT® network, of which 88 sites in 15 states, tracked the use and abuse of CHAT® Network prescription opioids including NUCYNTA® ER and contributed 1,388 adolescent assessments. Aproximately 77% of which (n = 1,063) were from participating sites in the state of Missouri. The states with the largest number of participating CHAT® sites during P1 2013 were Missouri (n = 40) and Michigan (n = 14). The majority of adolescents assessed were male (70.5%), Caucasian (67.6%), and between 15 and 18 years of age (77.5%). The majority (81.1%) reported usually living with one or both biological or adoptive parents. Approximately 82% of adolescents indicated current enrollment in a school program, the majority of whom (71.4%) reported enrollment in public school. Approximately 31% of the adolescent respondents reported that they were in a controlled environment (e.g., substance abuse treatment facility, juvenile detention center, etc.) in the 30 days prior to completion of the CHAT® assessment. 31.7% reported that they were currently taking a prescribed medication for emotional, behavioral, or learning problems. Current physical problems or illnesses were indicated by 28.9% and approximately 17.9% of adolescents reported a current problem with pain. One hundred twenty-four adolescents reported past 30-day abuse of any prescription opioid medication within the CHAT® network monitoring NUCYNTA® ER during P1 2013. No cases of past 30-day NUCYNTA® ER abuse was observed in the CHAT® network of sites monitoring NUCYNTA® ER during P1 2013.

- **Overall Summary**

Within the CHAT® network of sites tracking the use and abuse of prescription opioids, including NUCYNTA® ER, for Period 1, a total of 124 adolescents reported past 30-day abuse of any prescription opioid medication, none of whom reported abuse of NUCYNTA® ER. It is important to note that approximately 77% of all CHAT® assessments submitted during the current reporting period were identified from participating sites in the state of Missouri. Thus, the data reported here should not be generalized to reflect national trends.

3.1.5.3. Web Informed Services (WIS®) Internet Monitoring Archive

3.1.5.3.1. Objectives

WIS® Internet Monitoring is a systematic technology designed to monitor targeted prescription-medication-related message boards on the internet in real time and to archive search results. This archive is a proprietary NAVIPPRO® data source representing a unique and permanent resource, as message board moderators routinely delete old posts without a clear schedule or rationale. The monitored websites constitute a consistent, stable population of recreational drug abusers and their online communications. The Internet Monitoring archive provides access to an established cohort of individuals who can be defined by their drug abuse activities and characteristics. The Internet Monitoring archive does not include content from chat sites, weblogs, or any form of email communication.

3.1.5.3.2. Methods

- **Message Board Terminology**

  Several terms relevant to internet-based message board discussion are described below:

  - **Mention:** Any instance of a word, such as the name of a prescription medication or its synonym.
  - **Post:** A single message entered by one user.
  - **Author:** A username that writes a post within a thread. It should be noted that during a particular timeframe, some authors post only once, while others post many times. For example, a username posting once during March 2013 would be counted as a single author, as would someone posting 15 times during the same period.
  - **Thread:** A collection of posts, much like a conversation or discussion, on the same subject, displayed in chronological order. A thread generally begins with a specific post or question and includes all subsequent responses. The author who writes the first post in a thread is often referred to as the "original poster" or "OP."
  - **Forum:** A collection of threads that are grouped by overall topic. For example, a website might organize all drug-related threads into several forums to enable members to find conversation related to topics and drugs of interest quickly. Examples of forum names may include: opioids, heroin, or marijuana.
  - **Quote:** Many internet message boards allow authors to "quote" information from another post. This allows authors to reference

information and comments from other posts throughout a thread.

- **WIS Internet Monitoring Archive Sampling**

Structured Query Language (SQL) queries are designed to identify posts during the reporting period that match search-string criteria for tapentadol and the 4 comparator products. Search-string queries search the body of each post in the Internet Monitoring archive and contain correct spellings of the products as well as common misspellings, slang, and/or wildcard characters in order to identify as many relevant posts as possible. As monitoring continues and new trends emerge, search strings are modified to include new terminology and/or eliminate keywords that falsely identify posts as being related to the target and comparator products. Using these queries, counts of posts, threads, and authors discussing the target and comparator products are provided, and post information is pulled for coding (in regards to NUCYNTA® ER, the author of the post mentioned extended release NUCYNTA® specifically).

- **Quantitative Analysis**

A quantitative analysis was conducted on the Internet Monitoring archive to examine discussions occurring on monitored internet websites for tapentadol and the 4 comparators during the reporting period. Estimates of the level of internet discussion related to the comparators were reported as the total number of posts (single messages entered by one user), threads (collection of posts, much like a conversation or discussion, on the same subject, displayed in chronological order), and authors (usernames that write a post within a thread) identified during a specified time period (i.e., counts). Proportions were then calculated as the proportion of product-specific posts, threads, and authors per 100 posts, threads, and authors within the archive for a specified time period. Confidence intervals for each proportion were calculated at the 95% confidence level and, when appropriate (i.e., when the numerator, n, was less than 30), using a Poisson distribution. Statistical significance was defined as non-overlapping 95% confidence intervals.

Since these analyses were conducted for overall post, thread, and author counts and did not involve review of the content of all posts, it is possible that false positives are included in the results. A false positive is a post that is mistakenly identified as pertaining to a target or comparator product.

- **Qualitative Topic Analysis**

A qualitative topic analysis was performed on the total sample of NUCYNTA® ER-related posts written during the reporting period to highlight the level of discussion pertaining to different topics. Posts were coded into five topic categories: routes of administration, extraction techniques, procurement, negative consequences, and general (if the other four categories did not apply). Each post was then further subcategorized.

Due to the unstructured nature of message board content, many posts pertain to more than one topic area (e.g., posts that discuss extraction techniques also often mention an intended route of administration) and are assigned to each applicable category. As such, the categories are not mutually exclusive.

Counts of the 5 topic categories were calculated collectively for the current reporting period.

- **Selection of Interesting Posts**

A selection of interesting posts related to NUCYNTA® ER were presented to provide examples of the variety of discussions that took place on message boards during the reporting period. While posts presented in this section of the report were de-identified (i.e., identifying information, such as username, was removed) and profane language was redacted, no other content was altered.

3.1.5.3.3. Summary of Results

- **Quantitative Analysis**

For P1 2013, a quantitative analysis was conducted on the Internet Monitoring archive to examine discussion occurring on monitored internet websites. Estimates of the level of internet discussion were reported for posts, threads, and authors identified during a specified time period as counts and proportions. Key observations included that nearly 370,000 posts were written during P1 2013. Posts written during this period contained nearly 18,000 distinct threads and written by over 10,000 unique authors. During this period, tapentadol was discussed in 90 posts, contained within 42 distinct threads, and written by 61 unique authors. Posts are not mutually exclusive and may contain information for tapentadol, NUCYNTA®, and/or NUCYNTA® ER. Overall, tapentadol was discussed at a lower frequency than the comparator compounds: oxymorphone, immediate release

single-entity oxycodone, hydromorphone, and tramadol. Eighty-three were categorized as tapentadol-general; 1 referenced to NUCYNTA®; and 6 referenced NUCYNTA® ER.

- **Qualitative Topic Analysis**

Among the NUCYNTA® ER-related posts (n = 6) for P1 2013, 3 of the posts referenced routes of administration, 3 referenced sources of procurement, 2 referenced extraction techniques, and 2 referenced negative consequences.

Within the 3 NUCYNTA® ER route of administration-related posts, 2 referenced use of the product via an unspecified oral route of administration, 1 referenced snorting, 1 referenced intravenous injection, and 1 referenced rectal administration. Two NUCYNTA® ER-related posts mentioned extraction techniques; 1 mentioned a multi-step physical process and the other discussed a single-step chemical process, such as dissolving the product in an acidic solution. The 3 posts pertaining to procurement in relation to NUCYNTA® ER during P1 2013 referenced obtaining the product from one's own prescription. Within the 3 NUCYNTA® ER-related posts observed to mention negative consequences during P1 2013, 1 mentioned overdose, 1 mentioned withdrawal, and 1 mentioned physical concerns. Of the 52 tapentadol -related posts identified as general, the majority (n=42) were abuse-related, 3 were non-abuse-related posts, and 7 posts mentioned the product in the context of a quote. The 6 NUCYNTA® ER-related posts observed during P1 2013 did not reference the product in a general context.

- **Posts**

For P1 2013, posts specific to NUCYNTA® ER and NUCYNTA® were excluded from formal content analysis due to small sample sizes. During P1 2013, the largest proportion (P) of tapentadol-general posts referenced the compound in a mixed (P = 0.29) context, followed by those posts that provided unclear opinions (P = 0.25), endorsed the use of the compound (P = 0.21) and discouraged the use of the compound (P = 0.20). A lower frequency of posts discussed the compound in a non-abuse related manner (P = 0.04).

- **Overall Summary**

For P1 2013, ninety messages related to tapentadol were identified on the monitored websites during 01 January 2013 - 30 April 2013. Overall, tapentadol was discussed at a lower frequency than the comparators. Posts

are not mutually exclusive and may contain information for tapentadol, NUCYNTA®, and/or NUCYNTA® ER. Of the 90 tapentadol-related posts, 83 were categorized as tapentadol-general, 1 as NUCYNTA®, and 6 as NUCYNTA® ER. Conversation regarding tapentadol was mostly general and abuse-related in nature. Tapentadol-related discussion during the reporting period pertained to several topics including the compound's abuse potential and recreational value. Discussions related to possible extraction techniques were observed in the monitored websites. Additionally, as observed in previous reporting periods, discussions of the potential hallucinogenic effects as well as other side effects associated with tapentadol were also noted.

3.1.5.4. Overall Summary of Findings for All NAVIPPRO® Programs for P1 2013

- **Overall Summary**

NAVIPPRO® surveillance report for P1 2013 presents data from ASI-MV®, CHAT®, and WIS® Internet Monitoring archive. The findings from surveillance for tapentadol (with a focus predominately on NUCYNTA® ER for this report) through NAVIPPRO® data streams indicate that no cases of past 30-day NUCYNTA® ER abuse were observed in the ASI-MV® nor CHAT® network of sites monitoring NUCYNTA® ER. Furthermore, information from Internet Monitoring indicates that tapentadol-related discussion is low and that the tapentadol products are comparatively less attractive for abuse than the other monitored compounds. At this time, there is no discernible abuse pattern for the compound, and results comparing tapentadol to comparators should continue to be interpreted with caution. Continued monitoring is warranted.

Overall Conclusion of RADARS® and NAVIPPRO® Data

When the results of the RADARS® Programs are taken together with the NAVIPPRO® data set, the rates of abuse, misuse, and diversion of tapentadol ER appear low on a population basis when compared to the other Schedule II comparator opioids in both the general population as well as those with known aberrant drug behaviors. When data are adjusted for the number of patients filling a prescription (URDD), data from the RADARS® system showed upward trends in cases in the Drug Diversion, OTP and College Survey programs, whereas downward trends in the Poison Center and SKIP programs were observed. The number of endorsements of NUCYNTA® ER in each program remains low. The findings from surveillance for tapentadol

(with a focus predominately on NUCYNTA® ER for this report) through NAVIPPRO® data streams indicate no cases of past 30-day abuse of NUCYNTA® ER within the ASI-MV® and CHAT® networks. Furthermore, information from Internet Monitoring indicates that tapentadol-related discussion is low and that the tapentadol products are comparatively less attractive for abuse than the other monitored compounds. The NAVIPPRO® data set showed that there is not a discernible abuse pattern or significant internet discussion for tapentadol ER. Neither the RADARS® nor NAVIPPRO® programs identified geographic signals of abuse for tapentadol ER that require field research; however, the overall conclusion is that continued monitoring is required.

3.1.6. Overall Summary of Results from the Pharmacovigilance Plan

An overall summary of the results from all surveillance activities is presented by event in Table 15. A check mark in the table indicates that the event was reviewed within a particular database, and no new safety signal was identified. These results are discussed within the context of the overall SSP safety evaluation in Section 4.

Table 15: Summary of Results From US Tapentadol ER Surveillance Activities by Event of Interest

			RADARS						NAVIPPRO		
Event of Interest	**SCEPTRE**	**FDA AERS[a]**	**Opioid Treatment Program**	**Drug Diversion Network**	**Key Informant Network**	**Poison Center**	**College Survey**	**Field Research[b]**	**Addiction Severity Index**	**Health Assessment for Teens**	**Web Informed Services**
Accidental exposure	√	√									
Addiction	√	√									
Choking	√	√									
Death	√	√				√[c]					
Diversion	√	√		√							
Drug abuse and Intentional misuse	√	√	√	√	√	√	√[d]	As needed	√	√	√
Misuse (Off-label use)	√	√				√[e]		N/A			√
Misuse (Medication error)	√[f]	√									
Overdose	√[f]	√									
Pediatric cases	√	√									
and lactation	√	√									
Potential manufacturing complaints (Increased and Decreased potency)	√[f]	√									
Respiratory depression	√	√									
Seizure	√	√									
Serotonin syndrome	√[f]	√									

Table 15: Summary of Results From US Tapentadol ER Surveillance Activities by Event of Interest

Key: √=No new safety signal noted based on the data received; ER=Extended-release; FDA AERS=Food and Drug Administration's Adverse Event Reporting System; N/A=Not applicable (ie, event of interest unable to be monitored in the data source); NAVIPPRO=National Addictions Vigilance Intervention and Prevention Program; RADARS=Researched Addiction-Related Surveillance; SCEPTRE=Global Medical Safety Worldwide Safety Database

a: The use of FDA AERS data is primarily for determining potential signals related to demography and outcomes of spontaneous tapentadol cases reporting the events of interest that were targeted for monitoring.

b: If any 3-digit ZIP code is identified as a potential signal based on RADARS data within any 2 quarters of a 12-month period, then this is a signal that will be prioritized. Once the presence of a prioritized signal is determined, field research is initiated by Pinney Associates on behalf of the Company.

c: Based on data for intentional exposure cases.

d: The RADARS College Survey is not administered in the 2nd quarter

e: Based on the limited data on pediatric exposure available for the combined unintentional/other exposure category.

f: Increased reporting percentage in 2013Q1 which is possibly related to the small number of total cases reported thus far in the quarter. Not considered a safety concern at this time

4. OVERALL SAFETY EVALUATION

Based on the reviewed data from the surveillance activities for the events of interest (Table 15), no new safety signals were identified. The data supporting these conclusions are presented for each event in the sections below.

Accidental Exposure and Misuse (Off-Label Use)

SCEPTRE, FDA AERS, and RADARS® Poison Center Network program were used to monitor AEs of interest accidental exposure and misuse (off-label use). Cumulatively, 2 US cases of accidental exposure and 7 US cases of off-label use were retrieved from SCEPTRE. The trending analysis was performed for off-label use and demonstrated an indeterminate pattern. There were no US cases in the FDA AERS database as of 2012Q4 for accidental exposure and no cases for off-label use. Based on this limited data, no new safety signals were identified based on reviews of SCEPTRE and FDA AERS data.

Data from the RADARS® Poison Center Network program on calls Data from the RADARS® Poison Center Network program on calls categorized as unintentional/other exposures provide limited information on misuse, specifically, pediatric exposure. There were very few cases in the unintentional/other category for this period. No unique tapentadol ER signal for the AEs of death or pediatric exposure (intentional or otherwise) was suggested. Based on these limited data, no new safety signals were identified based on the review of Poison Center Network data.

Addiction

SCEPTRE, FDA AERS, the RADARS® programs (Opioid Treatment and Key Informant programs), and NAVIPPRO® programs (ASI-MV® and CHAT®) were used to monitor the event of interest addiction. Cumulatively, there were 2 US cases reporting addiction retrieved from SCEPTRE; hence, a trending analysis was not performed. There were no cases in the FDA AERS database as of 2012Q4 for addiction. Based on this limited data, no new safety signals were identified based on reviews of SCEPTRE and FDA AERS data.

Choking

SCEPTRE and FDA AERS were used to monitor the events of choking. Since product launch, 5 US cases reported choking in SCEPTRE, but the reporting trend for these cases is stable. Review of the individual cases did not suggest a safety concern. There was 1 case in the FDA AERS database as of 2012Q4 for this event. Based on this limited data, no new safety signals were identified based on reviews of SCEPTRE and FDA AERS data.

Death

SCEPTRE, FDA AERS, and the RADARS® Poison Center Network were used to monitor death. Since product launch, 6 US cases reported a fatal outcome in SCEPTRE, the reporting trend for these cases is stable. There were 8 cases reporting a fatal outcome in the FDA AERS database as of 2012Q4. Based on this limited data, no new safety signals were identified based on reviews of SCEPTRE and FDA AERS data.

Data from the RADARS® Poison Control Center Network on calls categorized as intentional exposures provides some potentially meaningful information given that there were no intentional or unintentional exposures with a fatal outcome during this review period.

Based on these limited data, no new safety signals were identified based on the review of Poison Center Network data.

Diversion

SCEPTRE, FDA AERS, and the RADARS® Drug Diversion Network were used to monitor diversion. Cumulatively, 3 US cases of diversion were reported from SCEPTRE, and hence a trending analysis was not performed. There was 1 case of diversion was reported from FDA AERS. Based on this limited data, a new safety signal was not identified.

Drug Abuse and Intentional Misuse

SCEPTRE, FDA AERS, and the RADARS® programs (Opioid Treatment Program, Key Informant Network, Poison Center Network, and College Survey Program) were used to monitor drug abuse and intentional misuse. Cumulatively, there were 4 US cases retrieved from SCEPTRE for drug abuse and intentional misuse, and hence a trending analysis was not performed. There were 4 cases in the FDA AERS database as of 2012Q4 for drug abuse and intentional misuse. Based on this limited data, no new safety

signals were identified based on reviews of SCEPTRE and FDA AERS data. Data retrieved from the RADARS® programs presented very few cases, and did not identify any unique tapentadol ER signal for drug abuse or intentional misuse. Based on these data sources, there does not appear to be a new safety signal.

Misuse (Medication Error)

SCEPTRE, FDA AERS, and the RADARS® Poison Center Network Program were used to monitor medication errors. Since product launch, 71 US cases reported medication errors in SCEPTRE, and the reporting for these cases increased in 2013Q1, 2013Q2, and 2013Q3. This increase is consistent with a recent change in case processing conventions. Case level review did not indicate any unusual patterns representing a signal. There were 8 cases in the FDA AERS database as of 2012Q4. Based on these data sources, there does not appear to be a new safety signal.

Overdose

SCEPTRE, FDA AERS, and the RADARS® Poison Center Network Program were used to monitor overdose. Cumulatively, there were 14 US cases retrieved from SCEPTRE for overdose, and the reporting trend was indeterminate. There were 6 cases in the FDA AERS database as of 2012Q4 for this event. Based on this limited data, no new safety signals were identified based on reviews of SCEPTRE and FDA AERS data.

Pediatric cases

SCEPTRE, FDA AERS, and the RADARS® Poison Center Network Program were used to monitor use in pediatric population. Since product launch, there were 2 US cases reporting use in the pediatric population in SCEPTRE. One case described a 15-year-old male who took 1 of his father's tapentadol ER 100 mg tablets. No adverse events were reported and the patient recovered from the accidental exposure. The second case described multiple patients whose mothers were treated with tapentadol hydrochloride (drug exposure via breast milk). There were no adverse reactions reported in this case. There were no cases in the FDA AERS database as of 2012Q4. In 2012Q4, 2013Q1, and 2013Q2, respectively, there were 4, 2, and 5 reports to the RADARS Poison Center of unintentional exposure to individuals aged 0 to 5 years, respectively, and no cases of unintentional exposure to individuals aged 6 to 12 years; all cases reported that patients recovered from

the exposure. Based on these data sources, there is not a new safety signal regarding use in pediatrics.

Pregnancy and lactation

SCEPTRE and FDA AERS were used to monitor use during pregnancy and lactation. Since product launch, there were 2 US cases describing use during pregnancy and lactation in SCEPTRE; these cases did not describe any AEs related to the pregnancy, outcome of the pregnancy or lactation. There were no cases in the FDA AERS database as of 2012Q4. Therefore, based on these data sources, there does not appear to be a new safety signal.

Decreased Potency

SCEPTRE and FDA AERS were used to monitor decreased potency. Since product launch, 130 US cases reported decreased potency in SCEPTRE, and the reporting trend for these cases was indeterminate. There were 13 cases in the FDA AERS database as of 2012Q4. Based on these data sources, there does not appear to be a new safety signal.

Increased Potency

SCEPTRE and FDA AERS were used to monitor reports of increased potency. Cumulatively, 7 US cases were retrieved from SCEPTRE for increased potency, and the reporting trend for these cases was stable. There were no cases in the FDA AERS database as of 2012Q4 for these events. Based on this limited data, no new safety signals were identified based on reviews of SCEPTRE and FDA AERS data.

Respiratory Depression

SCEPTRE and FDA AERS were used to monitor respiratory depression. Cumulatively, 5 US cases were retrieved from SCEPTRE for respiratory depression, and the reporting trend for these cases was stable. There were 6 cases in the FDA AERS database as of 2012Q4 for these events. Based on this limited data, no new safety signals were identified based on reviews of SCEPTRE and FDA AERS data.

Seizures

SCEPTRE and FDA AERS were used to monitor seizures. Since product launch, 7 US cases reported seizures in SCEPTRE and the reporting trend for these cases is stable. Review of the individual cases did not suggest a

safety concern. There were 3 cases of seizures retrieved from FDA AERS. Based on the data reviewed in these data sources, there does not appear to be a new safety signal.

Serotonin Syndrome

SCEPTRE and FDA AERS were used to monitor serotonin syndrome. Since the product launch, 21 US cases reported serotonin syndrome in SCEPTRE, and the reporting trend for these cases was indeterminate. Review of the individual cases did not suggest a safety concern. There were 15 cases of serotonin syndrome retrieved from FDA AERS. Based on the data reviewed in these data sources, there does not appear to be a new safety signal.

5. BENEFIT RISK CONCLUSIONS

This progress report evaluated data generated from the pharmacovigilance activities outlined in the SSP for tapentadol ER. Based on the newly generated data, the benefit risk conclusions remain favorable for tapentadol ER.

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